THE GENERAL HOSPITAL AND NURSING HOME AS A FOCAL POINT FOR TUBERCULOSIS CONTROL

Lawerence D. Edwards
Stuart Levin

ABSTRACT. Control of tuberculosis today should be centered in screening and treating patients in our general hospitals and nursing homes. The concept of breakdown or reactivation tuberculosis of the adult type presumes that the patient's ability to contain latent infection is impaired by other disease processes, particularly those that affect the lung or cellular immune defenses. Increase in use of steroids, immunosuppressive drugs, radiotherapy, the lengthening of the life span particularly in patients with malignancies as well as gastric surgery, make it more logical to approach control in the general hospital rather than in the tuberculosis sanatorium. Skin test conversion rates in hospital employees suggest that transmission of tuberculosis occurs with sufficient frequency that annual skin tests for all employees should be a routine procedure in hospitals. Furthermore, present available evidence indicates that most employees acquire their infections from unrecognized cases. Intensive education of hospital personnel is important. Screening of high-risk patients, including admission skin tests and sputum smears on those with productive cough, is indicated.

In the United States, tuberculosis case finding has traditionally been based in the community, i.e., screening of outpatients. Examples of such screening programs include mass chest x-rays and tuberculin skin testing programs in schools and industry.[1-4] More recent recommendations have suggested phasing out mass x-ray screening and restricting tuberculin skin testing screening only to school populations where the expected reactor rate is greater than 0.5 to 1.0 percent.[1,4-7] However, communities with the highest reactor rates are often the least responsive to these programs. Indeed, New York City health officials have settled for consent rates for skin tests and BCG administration rarely exceeding the 50 percent level.[1]

According to Stead's "unitary concept" of tuberculosis, one should expect breakdown of dormant tuberculosis foci to occur in patients with waning immunity due to aging or other intervening diseases.[8,9] Therefore, tuberculin reactors entering our general hospitals and nursing homes should be those at greatest risk of having or developing active tuberculosis.* These patients, if unrecognized, have the potential for spread of their disease to susceptible employees and other patients, thus completing the cycle for perpetuation of the organism by producing a new generation of patients, i.e., hospital employees with primary tuberculosis and the ensuing possibility of immediate disease or breakdown at a later date.

From the Section of Infectious Diseases of the Department of Internal Medicine, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois

Lawerence D. Edwards, M.D., Chief, Surveillance Unit; Assistant Attending Physician, Presbyterian-St. Luke's Hospital; Assistant Professor, Rush Medical College

Stuart Levin, Director of the Section of Infectious Diseases; Senior Attending Physician, Presbyterian-St. Luke's Hospital; Associate Professor, Rush Medical College

*Throughout this report, remarks made about the general hospital apply also to nursing homes with their concentration of the elderly and infirm.

It is the thesis of this paper that Sutton's law ("going where the money is") should be obeyed in tuberculosis case finding by initiating tuberculin skin testing in high-risk inpatients and all employees of our general hospitals and nursing homes. Positive reactors and their close contacts from the community can be followed and treated through a cooperative venture between the hospital or nursing home and the established agencies for tuberculosis control in the community.

Risk Factors in Hospitalized Tuberculin Reactors

Patients infected with Mycobacterium tuberculosis, with the greatest potential for developing active disease are: persons with inactive tuberculosis including ex-patients who have not had adequate drug therapy, persons with chest x-ray findings consistent with healed adult-type pulmonary tuberculosis and a positive skin test, recent skin-test convertors, patients with positive skin tests under the age of 20, and household contacts of known cases.[10] In addition, at increased risk are positive tuberculin reactors that receive steroids or immunosuppressive drugs, those with alcoholism, those undergoing gastrectomy, those with diseases affecting the reticuloendothelial system such as lymphomas, leukemia, or histoplasmosis, those with severe diabetes mellitus, with silicosis, with malignancies of any type, or that are elderly; and finally, children who are positive reactors who develop measles, polio, pertussis or receive the respective vaccines.[10-22]

There are two factors important in the breakdown of a previously quiescent tuberculous focus: (1) mechanical erosion and (2) a decrease in immune defenses, particularly cellular immunity. Both factors may be operative, e.g., the patient with brochogenic carcinoma may mechanically erode an old tuberculous focus, the malignancy itself may adversely affect the cellular immune response, and immunosuppressive therapy may further impair his immune defenses.[11-16]

Owing to the mobility of our population, infected patients may enter several different hospitals for treatment of tuberculosis or another disease. Whether or not these patients are identified as having tuberculosis will depend on their physical capability to respond (e.g., coma), their desire to report this information, and the expertise of the physician taking the history. These infected patients may enter the hospital with active disease. One recent series has reported 40 cases of active pulmonary tuberculosis with negative findings on chest x-rays.[23] Thus the admitting chest x-ray may not always be of help in determining activity of disease and less so, for those who break down late in their hospital course, i.e., those that may not become active until later in the hospital course after undergoing gastric surgery, steroid therapy, or immunosuppressive drug therapy for another disease.

One study in a general hospital with a tuberculosis ward revealed that 41 of 75 tuberculosis patients were on the general medical and surgical wards. These patients were not routinely isolated nor placed on chemotherapy early in their hospital course: a time when they had the potential of infecting other patients and employees.[24] The question is How often does this occur? The answer will vary from hospital to hospital depending on the latent infection rates in the population from which their patients are derived. Whereas rates are lowest in rural communities and highest in urban ghettos, approximately one-half of the total number of cases occur in communities with less than 100,000 population.[25] Part of this may be accounted for by the mobility of people who contract primary tuberculosis as youngsters in an urban setting and present with "breakdown" tuberculosis late in life in smaller communities to which they have migrated. Actually, rates will vary with subpopulations within hospitals since most hospitals care for patients from several socio-economic groups, and adverse sociologic

concomitants have been correlated with tuberculin sensitivity.[26,27] Specific rates for civilian hospital inpatients are not known since, to our knowledge, such studies have not been done.

Risk Factors for General Hospital Employees

An estimation of risk is available, however, from studies on skin test conversion rates of hospital employees who, in the majority of cases, presumably contract their disease from patients. In the preisoniazid era, most student nurses entering training with negative skin tests would convert to positive prior to their graduation. In one study 87 percent of these conversions occurred before the student's tuberculosis rotation, indicating the importance of the unrecognized tuberculosis patient as a source of infection.[28] More recent studies have documented annual conversion rates of approximately two percent of hospital employees in university and veterans' administration hospitals or a rate of 2,000/100,000 employees at risk.[29-31] It has been estimated that 8.5 percent of new infections will progress to clinical disease in the first year of infection.[32] This would result in an annual case rate of 170/100,000 (0.085 x 2000), a rate similar to that observed in the most poverty stricken neighborhoods in our larger cities.[1,29-31,33]

Such rates may vary with the type of hospital involved. A thorough study of 164 tuberculosis cases occurring in hospital employees in Ontario, from all types of hospitals, between 1966 and 1969, revealed a case rate of 33 per 100,000.[34] Over three-fourths of these cases occurred in general hospitals. Only 23 cases (14 percent) were recent convertors, twelve of whom had known recent contact with tuberculosis patients. Of one hundred and ten of these employees 66 had a history of a positive skin test only; 20 also had an abnormal chest x-ray; and 24 had a history of previous active tuberculosis. The preponderance of active disease in employees previously known to be infected suggests that activation by reinfection was likely. Rates were highest among hospital employees having close patient contact and lowest among those with remote contact (see table).

Should the Tuberculosis Patient be Cared for in the General Hospital?

In this day when specialized tuberculosis hospitals are being phased out in many areas, more and more known tuberculosis cases will be cared for in the general hospital.[35-40] Since many tuber-

COMPARATIVE ANNUAL PREVALENCE RATES FOR ACTIVE TUBERCULOSIS CASES PER 100,000 POPULATION IN SELECTED GEOGRAPHICAL AREAS AND VARIOUS HOSPITAL EMPLOYEE GROUPS

Hospital Employee Group*	Rate	Geographical Area**	Rate
.....	..	Iowa	5
Dietary and Clerical	16	Michigan	16
Student Nurses	18	Pennsylvania	18
Nurses other than Student or Graduate	31	Alabama	34
Graduate Nurses	55	District of Columbia	49
Radiology and Laboratory Technicians	60	.....	..
Medical Interns and Residents	81	Chicago, Illinois***	69
All Employees	33	United States	18

*Reference 34—average for the years 1966–1969.
**Reference 25—1970 data.
***Reference 33—1970 data.

culosis patients have other diseases also, it would seem more appropriate to provide comprehensive care for them in the general hospital.[41] Judging from the literature on skin test reactor rates in hospital employees, it should be evident that the general hospital has been "taking care of" unrecognized tuberculosis patients (during the period of greatest contagion) for some time. Thus, the question as to whether general hospitals should provide care for these patients is not so relevant since that is just what they have been doing, albeit in a poor manner.[42-43] It would be more appropriate to spend energy in educating general hospital employees as to how to identify and initiate care for the patient with tuberculosis.[41-46] This is the best way to minimize potential spread.

This is of particular concern due to the increasing use of steroids, radiation and immunosuppressive drugs which are likely to accelerate the rate of activity in patients with latent infection.[10-16] This may result in a leveling effect on the current decline in rates of tuberculosis. A word of caution must be interjected concerning acceptance of currently quoted skin test reactor rates in the United States. The possible use of unstabilized purified protein derivative (PPD) and its ensuing loss of potency from time in glass vials or plastic syringes may have resulted in falsely low rates in previous studies.[47-50]

Control Measures in the General Hospital Isolation Techniques

Precautions should be taken in all patients with a productive sputum, to prevent airborne spread of organisms, until such patients are proven free of active tuberculosis. The patient who is smear-positive and culture-positive is more infectious than the patient who is smear-negative and culture-positive.[51] Isolation techniques should include a single room with a door that can be closed, an exhaust system diverting air flow to the outside of the hospital, masks for patients and employees that screen out small particles (<0.5 microns) with instructions about properly fitted masks, cough control, and disposal of sputa.[52] Recirculation of air should be avoided.[35] Ultraviolet light, properly installed and maintained, may be of some help but usually is not practical for installation for all patients at risk.[36,39] Other forms of isolation are not necessary or desirable.

When patients at risk are transported for diagnostic procedures, mask, cough and sputa isolation techniques should be maintained. The high rate of disease in x-ray and laboratory technicians in the Ontario study emphasizes the necessity for this precaution[34] (see table).

Laboratory personnel handling sputa specimens should wear appropriate masks and have a hooded exhaust available to them for processing in order to avoid exposure during accidents which may result in viable aerosols.

Prosectors and observers at autopsy (medical students, laboratory technicians and others) are also at high risk when viable aerosols are created from the unrecognized tuberculosis case.[53,54] Proper masking, ventilation, particular attention to patients previously having productive coughs and positive skin tests, and care to minimize the number of observers in these cases all will help to reduce this risk.

Tuberculin Skin Tests

It is advocated that high risk patients have a skin test on the day of admission to the hospital with an appropriately placed 5 tuberculin unit-purified protein derivative (5 TU-PPD) stabilized with Tween 80.[47-50] The Tine test is not as reliable and is more difficult to read.[55,56] Also a quantitative reading of the 5 TU-PPD at 48-72 hours has prognostic significance. In one study patients with reactions greater than 15 mm had 2.5 times the rate of clinical disease as those with reactions of 9-15 mm.[57]

All employees should have tuberculin testing at the time of initial employment and annually thereafter if negative. The criterion of a negative test is an area of induration less than 10 mm after 72 hours, and 10 mm or greater for a positive reaction. If positive, evaluation for active disease should be done. If there is

no evidence for active disease prophylactic isoniazid should be considered as well as annual chest x-rays[58,59] (see below).

Practical Considerations for Skin Testing

One must be aware of false negative reactions induced by some live virus vaccines, steroids, immunosuppressives, aging, malignancies, use of non-stabilized PPD, as well as false positive reactions (so called conversions) due to blood transfusions (i.e., sensitized lymphocytes from a positive donor), previous skin testing with non-stabilized PPD, and the booster effect of skin testing in the elderly.[10-14,20-22,47-50,60]

Modification of the dose of PPD must be made for patients with a high index of suspicion for active tuberculosis where one may wish to start with 1 TU. Contrariwise, it has been documented that about 20 percent of patients with tuberculosis may not react at the 5 TU dose, and skin testing through 250 TU may be necessary, particularly for elderly patients.[20,61-63]

If the reaction is $<$ 10 mm at 5 TU and the index of suspicion for clinical disease is great, one should proceed to 100 TU; if the reaction is completely negative at 5 TU, one may proceed to 250 TU. The risk of intensive local reaction is minimal: about 1 per 1000 tests done in the past five years at a municipal contagious disease hospital where all admissions are routinely tested.[64]

Quantitative tuberculin skin reactions following BCG vaccination vary with the viable counts of the vaccine used.[65] While the quantitative reaction tends to wane with time, it still obscures the skin test as a reliable marker for tuberculosis infection.[66] Careful histories should be taken concerning BCG vaccination, its time of administration and post-vaccination skin test conversion.

Ferebee has discussed the logic of BCG versus isoniazid administration as the means of tuberculosis control in this country. While BCG may be justifiable in selected communities with known high tuberculin reaction rates, it does negate the value of the skin test as a screening tool. We agree that effective control can be achieved in the United States most speedily by treating positive reactors with isoniazid.[32]

After skin testing, the person should receive a card indicating the quantitative reaction, the date, and the dose of PPD used. This will allow for good judgment for possible retesting on a later admission as well as provide a tool for educating the patient about tuberculosis.

In order to standardize techniques of application and reading skin tests, we favor using a few trained personnel. Hospitals that employ nurse epidemiologists for infection surveillance and control may find them to be ideal for this task.[67] This nurse, in turn, should be responsible to a physician in the hospital knowledgeable about tuberculosis.

Prophylaxis with Isoniazid

All reactors who do not have evidence of active disease should be considered candidates for prophylactic isoniazid. Prophylactic isoniazid should definitely be administered to the high risk groups already enumerated.[10-22] Initially, active disease should be ruled out by evaluation of the following sites: pulmonary (chest film, sputum smear and culture); kidney (unexplained pyuria or hematuria indicating IVP and culture); bone (if the patient has specific chronic musculoskeletal complaints, x-rays, bone scan and biopsy may be indicated); unexplained lymphadenopathy (biopsy); and any other body area where the patient has specific unexplained complaints.[68,69]

Whether or not one uses isoniazid for chemoprophylaxis at a dose of 300 mgm once a day for one year depends on a consideration of the therapeutic to toxic ratio of the drug. Two examples serve to illustrate this concept. A recent convertor has an 8.5 percent chance of developing active disease in the first year of infection.[32] Isoniazid may reduce the incidence of active disease by 50 to 75 percent.[10] The toxicity of isoniazid has been

stated to be 0.2 to 0.4 percent.[70] Using the higher limits given the therapeutic/toxic ratio of the isoniazid for one year's treatment would be $\frac{8.5\% \times 0.75}{0.4\%} = 15.94$, or 16 chances of "helping" the patient, compared to one chance of "harming" him. The risk of developing active disease with the skin test positive and no other risk factor is one in 625 or 0.16 percent.[32] Thus, the therapeutic toxic ratio is: $\frac{0.16\% \times 0.75}{0.4\%} = \frac{0.3}{1.0}$ or one chance in helping the patient, versus about 3.3 chance of harming him. Furthermore, if the risk of active disease is 1 in 189 (0.53 percent), one has an equal chance of protecting the patient or having a toxic effect of the drug: $x = \frac{0.4\%}{0.75} = 0.53\%$

It is imperative that the patient be monitored for evidence of isoniazid toxicity.[10] A suggested outline has been given by the Ad Hoc Committee on Isoniazid and Liver Disease for hepatotoxicity.[70a] Besides liver disease related to isoniazid, memory difficulties, neuritis, acute isoniazid poisoning, vitamin B-6 deficiency and possibly increased toxicity in slow as compared to fast acetylators should all be considered in the monitoring program.[71-74]

Practical Considerations for Treatment

Three major anti-tuberculous drugs: isoniazid, rifampin and ethambutal have the advantage of a once-a-day oral dose ensuring greater patient cooperation during the one year of treatment (possibly longer in some patients with cavitary disease). Usually two of these drugs are used in one combination or another. Dose, side effects, and therapeutic effectiveness have been detailed in several studies.[75-80] The major drawback is the current costs of ethambutal and rifampin; although this argument is lessened if use of these drugs results in earlier discharge from the hospital.[75]

Special consideration should be given to patients contracting their disease in South Vietnam (or contacts of such patients) and retreatment cases who have not taken their medications regularly. In these patients rates of isoniazid resistance may be high.[81-87] In such cases primary treatment with rifampin and ethambutal can be given until sensitivities are obtained from the laboratory, if ethambutal has not been used in previous treatment.[75, 88-93]

It is important to realize that all patients with tuberculosis do not need hospitalization for treatment.[44,94] Furthermore, in the monkey, isoniazid has reduced tubercle bacilli from an inoculum of 10^6 to 10^7, down to 10^2 in a period of four weeks, whereas the two-log residium has not disappeared until another five months of treatment has been given.[95] Shedding of bacilli in the sputum is related to extent of disease but it is usual for most patients to have a declining count after two weeks of chemotherapy.[96] A patient should be ready for discharge when he is on effective chemotherapy and is smear-negative or has only a rare tubercle bacillus on smear.[96] Since household contacts should be placed on prophylactic isoniazid after evaluation to rule out active disease, early discharge of the patient with home treatment should be encouraged, provided one is not dealing with a potential isoniazid-resistant strain (i.e., a patient acquiring disease in the Far East, retreatment cases, or patients contracting their disease from these two groups).[97-99] This is preferable both for economic and social reasons. The family's cooperation in taking prophylactic isoniazid should be an inducement for the patient to take his medications faithfully.

REFERENCES

1. Richter ED: Tuberculosis control in the inner city. New York J Med **72**:625-629, 1972

2. Hanzel GD: A program for tuberculosis control in the schools. Amer J Public Health **60** 1238-1244, 1970

3. Curry FJ: Tuberculin skin testing in San Francisco schools, 1956-1966—an epidemiologic analysis Dis Chest **52**:361-370, 1967

4. Swallow J, Sbarbaro JA: Analysis of tuberculosis casefinding in Denver, Colorado, 1965-1970. Health Serv Report **87**:375-384, 1972

5. Robinson D: Routine tine test discontinued. New Eng J Med **286**:1060-1061, 1972

6. Edwards PQ, Ogasawara FR: Phasing out the child-centered TB program. Nat Tubercul Resp Dis Ass Bull Nov 1971

7. Katz J, Kunofsky S: Logistics of chemoprophylaxis of tuberculosis. Chest **59**:600-605, 1971

8. Stead WW: Pathogenesis of the sporadic case of tuberculosis. New Eng J Med **277**:1008-1012, 1967

9. Stead WW, Kerby GR, Schleuter DP, Jordahl CW: The clinical spectrum of primary tuberculosis in adults. Ann Int Med **68**:731-744, 1968

10. Preventive treatment of tuberculosis. A joint statement of the American Thoracic Society, National Tuberculosis and Respiratory Disease Association, and the Center for Disease Control. Amer Rev Resp Dis **104**:460-463, 1971

11. The Lancet: Radiation, immunity, and cancer. Lancet **II**:217-218, 1972

12. Han T: Immunosuppressive effect of surgery in patients with breast cancer. Clin Res **20**:566, 1972

13. Stjernsward J, Vanky F, Jondal M, Wigzell H, Sealy R: Lymphopenia and change in distribution of human B and T lymphocytes in peripheral blood induced by irradiation for mammary carcinoma Lancet **I**:1352-1356, 1972

14. Bonchek LI: Diagnosis of lung cancer in tuberculous patients. Chest **60**:256-259, 1971

15. Tunell WP, Koh YC, Adkins PC: The dilemma of coincident active pulmonary tuberculosis and carcinoma of the lung. J Thorac Cardiovasc Surg **62**:563-567, 1971

16. Neff TA, Ashbaugh DG, Petty TL: Miliary tuberculosis and carcinoma of the lung. Amer Rev Resp Dis **105**:111-113, 1972

17. Befeler B, Baum GL: Active pulmonary tuberculosis after upper gastrointestinal surgery. Amer Rev Resp Dis **96**:977-980, 1967

18. Wheldon EJ, Venables CW, Johnston ID: Late metabolic sequelae of vagotomy and gastroenterostomy. Lancet **I**:437-440, 1970

19. Goodwin RA, Snell JD, Hubbard WW, Terry RT: Relationships in combined pulmonary infections with histoplasma capsulatum and mycobacterium tuberculosis. Amer Rev Resp Dis **96**:990-997, 1967

20. Woodruff CE, Chapman PT: Tuberculin sensitivity in elderly patients. Amer Rev Resp Dis **104**:261-263, 1971

21. Pieroni RE, Stevens DL, Stojanovic A, Levine L: Investigation of the responsiveness of BCG-vaccinated children with whooping-cough to tuberculin. Int Arch Allerg **42**:583-589, 1972

22. Berkovich S, Starr S: Effects of live type 1 poliovirus vaccine and other viruses on the tuberculin test. New Eng J Med **274**:67-72, 1966

23. Husen L, Fulkerson LL, Del Vecchio E, Zack MB, Stein E: Pulmonary tuberculosis with negative findings on chest xray films—a study of 40 cases. Chest **60**:540-542, 1971

24. Edwards LD: Infections and use of antimicrobials in an 800-bed hospital. Public Health Rep **84**:451-457, 1969

25. Reported tuberculosis data 1970. A summary for the United States of statistical data reported on tuberculosis in 1970. DHEW publication No. (HSM) 72-8096 (January) 1972

26. Kuemmerer JM, Comstock GW: Sociologic concomitants of tuberculin sensitivity. Amer Rev Resp Dis **96**:885-892, 1967

27. Lester W: Tuberculosis—an urban problem. Ann Int Med **68**:947-949, 1968

28. Levine I: Tuberculosis risk in students of nursing. Arch Int Med **121**:545-548, 1968

29. Szent-Gyorgyi N: Risk of tuberculous infection and of radiation among university students. Amer Rev Resp Dis **83**:432-435, 1961

30. Riley RL; The hazard is relative. Editorial, Amer Rev Resp Dis **96**:623-625, 1967

31. Atuk NO, Hunt EH: Serial tuberculin testing and isoniazid therapy in general hospital employees. JAMA **218**:1795-1798, 1971

32. Ferebee SH: An epidemiological model of tuberculosis in the United States. Nat Tubercul Ass Bull (January) 1967

33. Rates for newly reported active-probably active cases of tuberculosis (all forms)—Chicago 1970 by community area and race. Statistical section the Tuberculosis Institute of Chicago and Cook County. (July) 1971

34. Ashley MJ, Wigle WD: The epidemiology of active tuberculosis in hospital employees in Ontario, 1966-1969. Amer Rev Resp Dis **104**:851-860, 1971

35. Ehrenkranz NJ, Kicklighter JL: TB outbreak in a general hospital—evidence for airborne spread of infection. Ann Int Med **77**:337-382, 1972

36. Statement on care of patients with pulmonary tuberculosis in general hospitals. Board of Trustees of the American Hospital Association. JAHA **46**:66, 122-124, 1972

37. Tuck J, Tyler JM: The present status of the admission of patients with tuberculosis to general hospitals. Amer Rev Resp Dis **101**:108-111, 1970

38. Tuberculosis and the general hospital. Massachusetts Department of Public Health. New Eng J Med **285**:352, 1971

39. Ad Hoc Committee on the treatment of tuberculosis patients in general hospitals. Guidelines for the general hospital in the admission and care of tuberculosis patients. Amer Rev Resp Dis **99**:631-633, 1969

40. Dandoy S, Elman SB: Current status of general hospital use for tuberculosis patients in the United States. Amer Rev Resp Dis **106**:580-586, 1972

41. NTA Ad Hoc Committee on treatment of TB patients in general hospitals, Infectiousness of tuberculosis. Amer Rev Resp Dis **96**:836-837, 1967

42. Jacobs S, Greenberg HB: Diagnosis and treatment of 20 tuberculous patients who entered a community hospital. Amer Rev Resp Dis **105**: 528-531, 1972

43. Ashba JK, Boyce JM: Undiagnosed tuberculosis in a general hospital. Chest **61**:447-451, 1972

44. Ad Hoc Committee on quality care for tuberculosis. Standards for tuberculosis treatment in the 1970's. Amer Rev Resp Dis **102**:992-995, 1970

45. Weg JG: Tuberculosis and the generation gap. Amer J Nurs **71**:495-500, 1971

46. Barham VZ: Changing the attitudes of hospital nurses. Nurs Outlook **19**:538-540, 1971

47. Landi S, Held HR, Tseng MC: Disparity of potency between stabilized and nonstabilized dilute tuberculin solutions. Amer Rev Resp Dis **104**:385-392, 1971

48. Zack MB, Fulkerson LL, Stein E: Clinical evaluation of persons positive to stabilized tuberculin but negative to nonstabilized tuberculin. Chest **60**:437-440, 1971

49. Edwards PQ: Tuberculin negative? New Eng J Med **286**:373-374, 1972

50. Third conference on evaluation of procedures for tuberculin testing. USPHS Center for Disease Control. (May) 1971

51. Narain R, Subba Rao MS, Chandrasekhar P, Pyarelal: Microscopy positive and microscopy negative cases of pulmonary tuberculosis. Amer Rev Resp Dis **103**:761-772, 1971

52. Riley RL, O'Grady O: Airborne infection—transmission and control. New York, MacMillan Co., 1961

53. Tuberculosis in the laboratory. Editorial. Lancet **II**:1023, 1970

54. Alpert ME, Levison ME: An epidemic of tuberculosis in a medical school. New Eng J Med. **272**:718-721, 1965

55. Browder AA, Griffon AL: Tuberculin tine tests on medical wards. Amer Rev Resp Dis **105**: 299-301, 1972

56. Hull FE: Tuberculin tine test. JAMA **203**: 120-126, 1968

57. Curry FJ: Prophylactic effect of isoniazid in young tuberculin reactors. New Eng J Med **277**:562-567, 1967

58. Committee on Therapy, American Thoracic Society. Personnel tuberculosis control program in medical institutions. Amer Rev Resp Dis **104**:463-465, 1971

59. Moulding T: Chemoprophylaxis of tuberculosis—when is the benefit worth the risk and cost? Ann Int Med **74**:761-770, 1971

60. Mohr JA, Killebrew L, Muchmore HG, Felton FG, Rhoades ER: Transfer of delayed hypersensitivity. JAMA **207**:517-519, 1969

61. Duboczy BO: Practical significance of booster effect of delayed type of skin test. Amer Rev Resp Dis **103**:719-721, 1971

62. Hyde L: Clinical significance of the tuberculin skin test. Amer Rev Resp Dis **105**:453-454, 1972

63. Holden M, Dubin MR, Diamond PH: Frequency of negative intermediate-strength tuberculin sensitivity in patients with active tuberculosis. New Eng J Med **285**:1506-1509, 1971

64. Levin S, Edwards LD: Unpublished data from Municipal Contagious Diseases Hospital, Chicago, Illinois, 1966-1972

65. Ashley MJ, Siebenmann CO: Tuberculin skin sensitivity following BCG vaccination with vaccines of high and low viable counts. Canad Med Ass J **97**:1335-1339, 1967

66. Comstock GW, Edwards LB, Nabangxang H: Tuberculin sensitivity eight to fifteen years after BCG vaccination. Amer Rev Resp Dis **103**:572-575, 1971

67. Edwards LD, Levin S, Lepper MH: Descriptive epidemiology. JAHA **45**:75-79, 1971

68. Carr DT, Karlson AG, Miller WE: Clues to discovery of pulmonary tuberculosis. Minnesota Med **54**:319-320, 1971

69. Davidson PT, Horowitz I: Skeletal tuberculosis—a review with patient presentations and discussion. Amer J Med **48**:77-84, 1970

70. Ad Hoc Committee: Chemoprophylaxis for the Prevention of Tuberculosis. Amer Rev Resp Dis **96**:558-560, 1967

70a. Ad Hoc Committee on Isoniazid and Liver Disease. Isoniazid and liver disease. Amer Rev Resp Dis **104**:454-459, 1971

71. Olsen PZ, Torning K: Isoniazid and loss of memory. Scand J Resp Dis **49**:1-8, 1968

72. Levy L, Higgins LJ, Burbridge TN: Isoniazid-induced vitamin B_6 deficiency—metabolic studies and preliminary vitamin B_6 excretion studies. Amer Rev Resp Dis **96**:910-917, 1967

73. Brown CV: Acute isoniazid poisoning. Amer Rev Resp Dis **105**:206-216, 1972

74. Jeanes CW, Schaefer O, Eidus L: Inactivation of isoniazid by Canadian Eskimos and Indians. Canad Med Ass J **106**:331-335, 1972

75. Loudon RG: The place of rifampin. Chest **61**:524-525, 1972

76. Schonell M, Dorken E, Grzybowski S: Rifampin. Canad Med Ass J **106**:783-786, 1972

77. Nitti V, Catena E, Delli Veneri F, De Michele G, Marra A: Rifampin in association with isoniazid, streptomycin, and ethambutol, respectively, in the initial treatment of pulmonary tuberculosis. Amer Rev Resp Dis **103**:329-337, 1971

78. Newman R, Doster B, Murray FJ, Ferebee S: Rifampin in initial treatment of pulmonary tuberculosis. Amer Rev Resp Dis **103**:461-476, 1971

79. Bobrowitz ID; Ethambutol in tuberculous meningitis. Chest **61**:629-632, 1972

80. Lees AW, Allan GW, Smith J, Tyrrell WF, Fallon RJ: Isoniazid and ethambutal in previously untreated patients with pulmonary tuberculosis. Amer Rev Resp Dis **105**:135-136, 1972

81. Poffenbarger PL: Tuberculosis in South Vietnam. Amer J Trop Med **21**:226-232, 1972

82. Stead WW, Bates JH: Primary tuberculosis from the Far East. Ann Int Med **70**:707-711, 1969

83. Cowley RG: Implications of the Vietnam war for tuberculosis in the United States. Arch Environ Health **21**:479-480, 1970

84. Steiner M, Cosio A: Primary tuberculosis in children—incidence of primary drug-resistant disease in the 332 children—observed between the years 1961 and 1964 at the Kings County Medical Center of Brooklyn. New Eng J Med **274**:755-759, 1966

85. Steiner M, Chaves AD, Lyons HA, Steiner P, Portugaleza C: Primary drug-resistant tuberculosis—report of an outbreak. New Eng J Med **283**:1353-1358, 1970

86. Isoniazid-resistant strains of M. tuberculosis. Letter to the Editor. Amer J Public Health **60**:612-617, 1970

87. Hobby GL, Johnson PM, Boytar-Papirnyik V: Primary drug resistance—a continuing study of drug resistance in tuberculosis in a veteran population within the United States. Amer Rev Resp Dis **103**:842-844, 1971

88. Raleigh JW: Rifampin in treatment of advanced pulmonary tuberculosis. Amer Rev Resp Dis **105**:397-408, 1972

89. Pines A: Results after retreatment of advanced pulmonary tuberculosis with rifampin and other drugs. Amer Rev Resp Dis **104**:126-127, 1971

90. Vall-Spinosa A, Lester W, Moulding T, Davidson PT, McClatchy JK: Rifampin in the treatment of drug-resistant Mycobacterium tuberculosis infections. New Eng J Med **283**:616-621, 1970

91. Hobby GL, Lenert TF: Observations on the action of rifampin and ethambutol alone and in combination with other antituberculous drugs. Amer Rev Resp Dis **105**:292-295, 1972

92. Lees AW, Allan GW, Smith J, Tyrrell WF, Fallon RJ: Re-treatment of pulmonary tuberculosis with rifampin and ethambutol. Amer Rev Resp Dis **105**:129-131, 1971

93. Jeanes CW, Jessamine AG, Eidus L: Treatment of chronic drug-resistant pulmonary tuberculosis with rifampin and ethambutol. Canad Med Ass J **106**:884-888, 1972

94. Tuberculosis Chemotherapy Centre, Madras. A concurrent comparison of home and sanatorium treatment of pulmonary tuberculosis in south India. Bull WHO **21**:51-144, 1959

95. Schmidt LH: Improving existing methods of control of tuberculosis—a prime challenge to the experimentalist. Amer Rev Resp Dis **105**:183-205, 1972

96. Committee on Bacteriologic Standards for the discharge of patients, American Thoracic Society. Bacteriologic standards for the discharge of patients. Amer Rev Resp Dis **102**:470-473, 1970

97. Ferebee SH: Isoniazid prophylaxis for the few? Or the many? Nat Tubercul Resp Dis Bull (October) 1968

98. Comstock GW, Ferebee SH, Hammes LM: A controlled trial of community-wide isoniazid prophylaxis in Alaska. Amer Rev Resp Dis **95**:935-943, 1967

99. Jenkins D, Davidson FF: Isoniazid chemoprophylaxis of tuberculosis. Calif Med **116**:1-5 1972

STUDIES ON THE PRIMARY STRUCTURE OF HUMAN SERUM TRANSFERRIN: A PRELIMINARY REPORT

ANATOLY BEZKOROVAINY
DIETMAR GROLICH

Transferrin is a non-heme iron-binding serum protein that serves the vital function of distributing iron throughout the human organism. It provides the vehicle whereby iron is transferred from the wall of the gastrointestinal tract into the circulation, it transfers the iron to its storage sites in the liver (in the form of ferritin and hemosiderin), it is required for the proper assimilation of iron by the immature red cells for the purpose of hemoglobin synthesis, and it acts as an iron acceptor following the catabolism of heme in the reticuloendothelial system. It is important, therefore, to know the structure of this protein, so that the molecular basis for these biological interactions can eventually be elucidated.

Information is already available on many aspects of the structure of transferrin, and this laboratory has already had occasion to report on our contributions to this field.[1] It has been recognized, however, that further progress will be made only upon the complete elucidation of the primary structure of transferrin, so that the segments of the molecule responsible for the binding of iron, for the interaction with erythrons, and for the interactions with the liver and intestinal cells can be accurately pinpointed. This task is of monumental proportions, since transferrin represents a single-chain protein with a molecular weight of near 80,000, and no protein of this size has yet been sequenced. This paper describes the results of studies in this direction made in our laboratory.

The standard procedure for the initiation of amino acid sequence studies of proteins involves the fragmentation of the protein by proteolytic enzymes or by chemical means. We chose to approach the problem by fragmenting the protein with cyanogen bromide (CNBr), a reagent that breaks those peptide bonds where the carboxyl groups are contributed by methionine residues. Transferrin is known to have eight methionine residues, hence a maximum of nine fragments would have been expected if this reagent were used. Each fragment, in turn, would then be subfragmented by enzymes such as trypsin, and the amino acid sequence of each fragment

From the Department of Biochemistry, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois

This work was largely supported by the Chicago Heart Association.

Anatoly Bezkorovainy, Ph.D., Associate Professor, Rush Medical College

Dietmar Grohlich, B.S., Research Assistant, Department of Biochemistry

eventually would be determined. In addition, it was hoped that there would be fewer fragments than the maximum of nine, i.e., that transferrin would have repeating peptide fragments within its polypeptide chain.

This possibility was predicted for many years on the basis of the fact that transferrin contains two oliogosaccharide (carbohydrate) chains and has two identical, but independent, iron-binding sites. At first, the existence of two identical subunits of a molecular weight of 40,000 each was reported.[2] However, our laboratory proved this to be incorrect.[3] Next, a report appeared indicating that conalbumin, a homologous protein from egg white, was split into only three fragments by CNBr, whereas a maximum of six were expected from its methionine content.[4]

More recently, it was reported that transferrin from the hagfish, an aquatic animal below the shark in the evolutionary tree, had a transferrin whose molecular weight was only 40,000 and which bound only one iron atom per protein molecule[5]. This led to the belief that transferrins arose through a gene duplication process and that the modern transferrin molecule consists of two identical or nearly identical halves. However, our laboratory was able to report, early in 1972, that the situation was not as simple as that: human serum transferrin, when split by CNBr, next succinylated to avoid nonspecific aggregation, then reduced-alkylated to break disulfide bonds, and finally, subjected to starch gel electrophoresis yielded a minimum of five fragments with different molecular weights and amino acid compositions.[6] And most recently, another laboratory reported that hagfish transferrin did not, after all, have a molecular weight of 40,000, and instead, was just as large as human transferrin.[7] It is clear that if transferrin had indeed arisen by a gene duplication process, the event must have occurred very far down the evolutionary tree, so that subsequent mutations had time to abolish most, if not all, similarities among the originally repeating polypeptide chain segments.

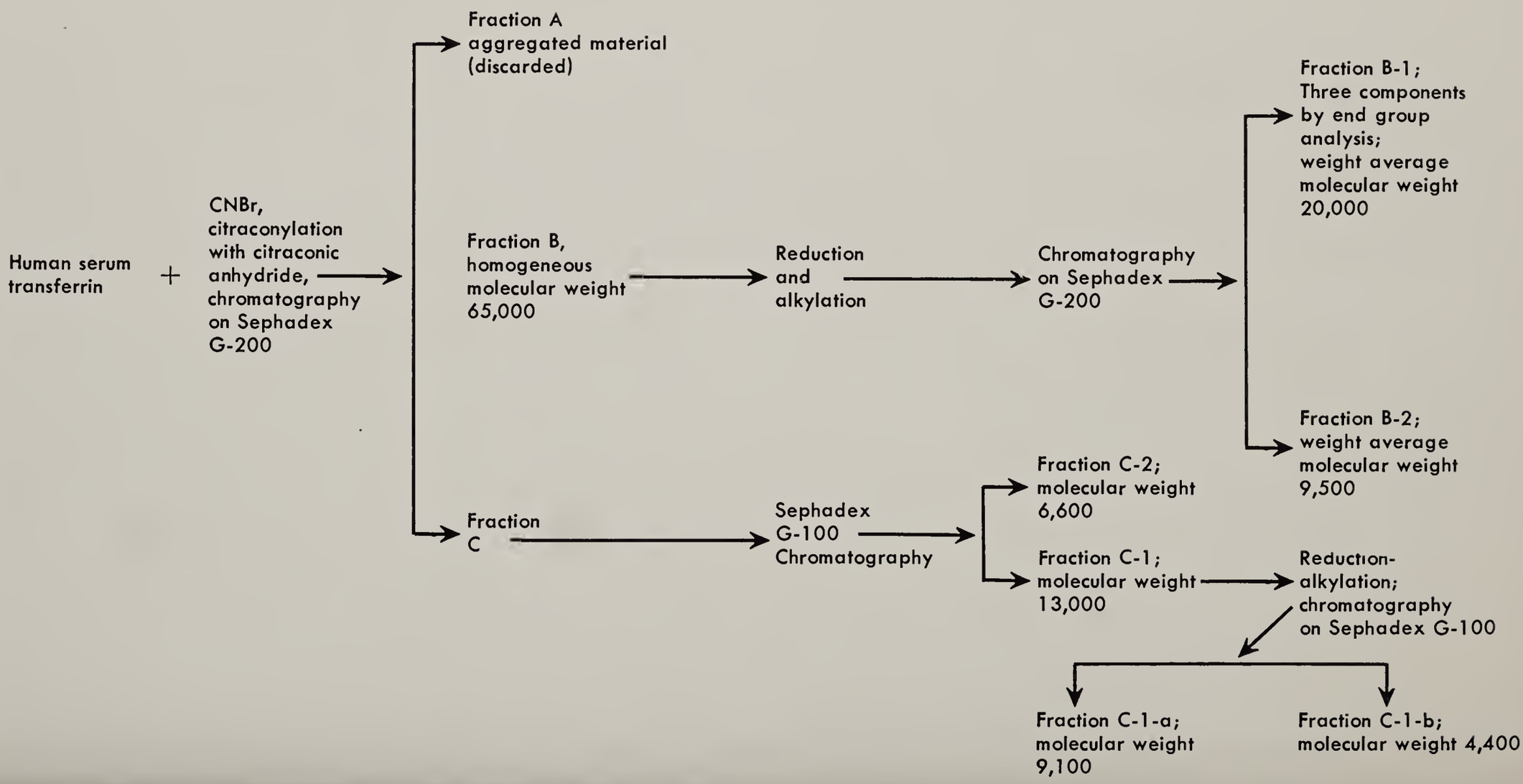
Since our last report on this subject,[6] we have been able to demonstrate the presence of at least seven of the possible nine fragments that can be produced from transferrin by CNBr, and have isolated four of them in a homogenous form. The diagram provides the scheme whereby this was accomplished. The last two fragments may eventually be shown to exist *via* techniques that have not yet been employed, or else there may indeed exist segments in the polypeptide chain of transferrin which have identical amino acid sequences.

Fractions isolated by the technique shown in the diagram (B-1, B-2, C-1-a, C-1-b and C-2) were subjected to starch gel electrophoresis, and B-2, C-2, C-1-a, and C-1-b were shown to be homogeneous. All fractions were de-acylated by mild acid hydrolysis (the citraconyl groups were removed), and all were subjected to N-terminal group analysis. Fractions B-2, C-1-a, and C-1-b had N-terminal aspartic acid, lysine, and valine respectively, hence fraction C-1-b represented the N-terminal fragment of the transferrin molecule. Fraction B-1 had N-terminal aspartic acid, glycine, and serine, hence it consisted of three components. It is thus clear that seven distinct fragments, *i.e.*, the homogeneous B-2, C-2, C-1-a, and C-1-b, and the three-component B-1, have been shown to be available from transferrin by CNBr cleavage.

Another interesting finding was the fact that half the carbohydrate originally present in transferrin could be accounted for in fraction B-1, and the other half in fraction B-2. This suggests that the two carbohydrate chains present in transferrin are not attached to polypeptide chains of identical amino acid sequences

Work is now in progress to resolve fragment mixture B-1, and when this is accomplished, to align all fragments in the sequence that exists in the native transferrin molecule. We will then be ready to embark upon the determination of amino acid sequences in each individual fragment.

FRAGMENTATION OF HUMAN SERUM TRANSFERRIN BY CYANOGEN BROMIDE AND THE ISOLATION OF FRAGMENTS PRODUCED. CITRACONYLATION INDICATES REACTION WITH CITRACONIC ANHYDRIDE TO PREVENT NON-SPECIFIC AGGREGATION OF FRAGMENTS PRODUCED. REDUCTION-ALKYLATION INDICATES THE CLEAVAGE OF DISULFIDE BONDS WITH MERCAPTOETHANOL, FOLLOWED BY THE ALKYLATION OF SULFHYDRIL GROUPS RELEASED BY IODOACETIC ACID.


Human serum transferrin
+
CNBr, citraconylation with citraconic anhydride, chromatography on Sephadex G-200
Fraction A aggregated material (discarded)
Fraction B, homogeneous molecular weight 65,000
Reduction and alkylation
Chromatography on Sephadex G-200
Fraction B-1; Three components by end group analysis; weight average molecular weight 20,000
Fraction B-2; weight average molecular weight 9,500
Fraction C
Sephadex G-100 Chromatography
Fraction C-2; molecular weight 6,600
Fraction C-1; molecular weight 13,000
Reduction-alkylation; chromatography on Sephadex G-100
Fraction C-1-a; molecular weight 9,100
Fraction C-1-b; molecular weight 4,400

SUMMARY

In our continuing study of the primary structure of transferrin we have been able to demonstrate the presence of seven of the possible nine fragments that can be produced by CNBr cleavage, and have isolated four of them in homogeneous form. Further work leading to determination of amino acid sequences in individual fragments is in progress.

REFERENCES

1. Bezkorovainy A: Transferrin, the central figure in the metabolism of iron by man. A progress report. Pres-St. Luke's Med Bull **9**:6, 1970

2. Jeppsson JO: Subunits of human transferrin. Acta Chem Scand **21**: 1686, 1967

3. Bezkorovainy A, Grohlich D: The behavior of native and reduced-alkylated human transferrin in urea and guanidine-HCl solutions. Biochim Biophys Acta **147**:497, 1967

4. Phillips JL, Azari P: On the structure of ovotransferrin. Isolation and characterization of the cyanogen bromide fragments and evidence for a duplicate structure. Biochemistry **10**:1160, 1971

5. Palmour RM, Sutton HE: Vertebrate transferrins. Molecular weights, chemical compositions, and iron-binding studies. Biochemistry **10**:4026, 1971

6. Bezkorovainy A, Grohlich D: Cleavage of transferrin by cyanogen bromide. Biochim Biophys Acta **263**:645, 1972

7. Aisen P, Leibman A, Sia CL: Molecular weight and subunit structure of hagfish transferrin. Biochemistry **11**:3460, 1972

SYMPATHECTOMY REVISITED: RETROSPECT AND PROSPECT

Geza de Takats

ABSTRACT. The author reviews his experience with sympathetic denervation for the last forty years and discusses the value of this procedure in apoplexy, angina pectoris, calcareous pancreatitis, essential and renal hypertension, peripheral vascular stenosis, Raynaud's phenomena, and causalgic states. The recent interest in the use of drugs effecting catecholamine release or blocking alpha and beta sympathetic receptors points to the potentialities of a regional denervation by sympathectomy as contrasted by a partially effective diffuse sympathetic paralysis induced by drugs.

INTRODUCTION

In 1939, my co-workers and I described the activities of a neurocirculatory clinic established at the University of Illinois.[1] We were naturally deeply influenced by the writings of René Leriche who focussed so much attention on the role of the autonomic nervous system in the perverted physiology of arterial disease.[2]

Subsequently, my co-workers and I reported on sympathetic blockade in apoplexy,[3] on sympathectomy for angina pectoris,[4] for the intractable pain of calcareous pancreatitis,[5] to increase the sugar tolerance of diabetics,[6] for essential and renal hypertension,[7] for peripheral vascular sclerosis,[8] for Raynaud's phenomena,[9] and for causalgic states.[10]

Much of this activity may well seem antiquated or inappropriate to the present generation. It seemed intriguing therefore to take a quick glance at present therapeutic trends in these areas, since so much pharmacologic effort is being expended today on the blockade of alpha and beta receptors and on the inhibition of catecholamine releasers. The possibilities of releasing sympathetic tone by injection or surgical removal will be reviewed and correlated with more recent physiologic and pharmacologic effects of sympathetic interruption on selected disease entities.

APOPLEXY

When the late N. C. Gilbert and I reported on a small group of apoplectic patients in whom the cervical sympathetic trunk was blocked on the ipsilateral side,[3] a loud chorus of opposition and disbelief became audible and I hastily summarized these arguments.[11] A distinguished neurologist wrote that the proponents of this method were "victims of an infectious epidemic of credulity and self deception."[12]

This response was understandable. Cerebral circulation was regarded as being controlled by the height of blood pressure and by tissue metabolites, notably the potent vasodilator, CO_2. Neurogenic control of cerebral circulation was believed to be minimal, cerebral vasospasm a myth. The constrictor activity of the vessels of the *pia mater* was said to be one-tenth that of the skin. Cerebral

From the Department of Cardiovascular-thoracic Surgery, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois

Geza de Takats, M.D., M.Surg. (Budapest), Emeritus Professor of Surgery, Abraham Lincoln School of Medicine and Rush Medical College; Consulting Surgeon, Presbyterian-St. Luke's Hospital

Presented at the Fall Meeting of the Illinois Surgical Society, at Urbana, Illinois, October 20, 1972

blood flow was just beginning to be measured by Kety's nitrous oxide method and showed no increase in global cerebral circulation in normal or hypertensive individuals after sympathetic block. On the contrary, known cerebral vasodilators, such as increased CO_2, decreased O_2, histamine, acetylcholine, nicotinic acid and papaverine showed a measurable increase in cerebral circulation with the nitrous oxide method.[13]

In spite of our early efforts with 79 personal and a collected series of 462 cases which showed a 65 percent clinical improvement, the method disappeared from sight.

With the advent of cerebral angiography, which created vehement opposition among some neurosurgeons, of isotope clearance methods and of sampling of spinal fluid for lactic acid, a number of points began to emerge. Focal ischemia of the brain, just as in other acutely ischemic parts of the body, is surrounded by vasoparalysis and edema. The vessels do not respond to CO_2 or O_2. The uninvolved part of the brain showed either edema with vasoconstriction or an immense reactive hyperemia, the luxury perfusion of Lassen, which is seen on release of arterial obstruction anywhere but seems far more menacing in a closed cavity with soft compressible cerebral tissue.[14]

Even a cerebral steal was discovered on vasodilation with CO_2 or papaverine, drawing blood away from the ischemic infarct. All these and many other fascinating facets of this problem have been aired in a symposium on cerebral blood flow.[15]

Much of what we suspected or speculated on in the early fifties has now acquired solid experimental basis. When the cerebral infarct develops, collateral circulation, both in the internal and the external carotids becomes active. Sympathetic block is known to decrease collateral resistance. Secondly, by lessening the edema the irreversibly lost area demarcates faster, not unlike a frostbitten gangrenous toe, with a proximal vasoparalysis and edema. Thirdly, by limiting the loss of adrenergic vascular tone to the infarcted side, the possibility of steal is localized to the infarcted side, where it helps to counteract metabolic acidosis.

One of the most significant studies relating to our present problem is that of John Stirling Meyer and his associates on the reduction of blood flow in the uninvolved contralateral hemisphere, in patients with unilateral cerebral infarction.[16] The analogy with the vascular effects of pulmonary embolism in the unaffected areas of the lung[17] is apparent. Whether this is a vasomotor effect or serotonin release can well be argued; however, the rapid recovery of hemispheric blood flow and metabolism in the younger age group make it desirable that blood flow be increased through all available channels. Venoconstriction, to my knowledge, has not been studied in cerebral infarction, but serotonin-release would affect it.

It thus becomes apparent that a restudy of the effect of unilateral and possibly bilateral cervical sympathetic blocks, performed within the first few but hardly more than 48 hours after the vascular insult is now in order, monitored by electroencephalogram,* regional flow studies and Technetium uptake. In this early phase, the use of papaverine, CO_2, hyperventilation, and carotid endarterectomy may well increase damage because of loss of autoregulation, vasoparalysis and edema in and around the area of infarction. Since hemorrhage, especially subarachnoid hemorrhage, is such a potent stimulus for vasospasm, the old arguments against sympathetic blockade in apoplexy may well need revision. It should be emphasized that this is meant to be an emergency measure, and the long-term treatment of stroke is an entirely different problem. None of the presently used emergency measures, such as vasodilators, vasoconstrictors, hyperventilation, hypoventila-

*I have published one such tracing, showing improvement of tracing within 15 minutes. Postgrad. Med. **5**:184-190, March, 1949 (Fig. 1).

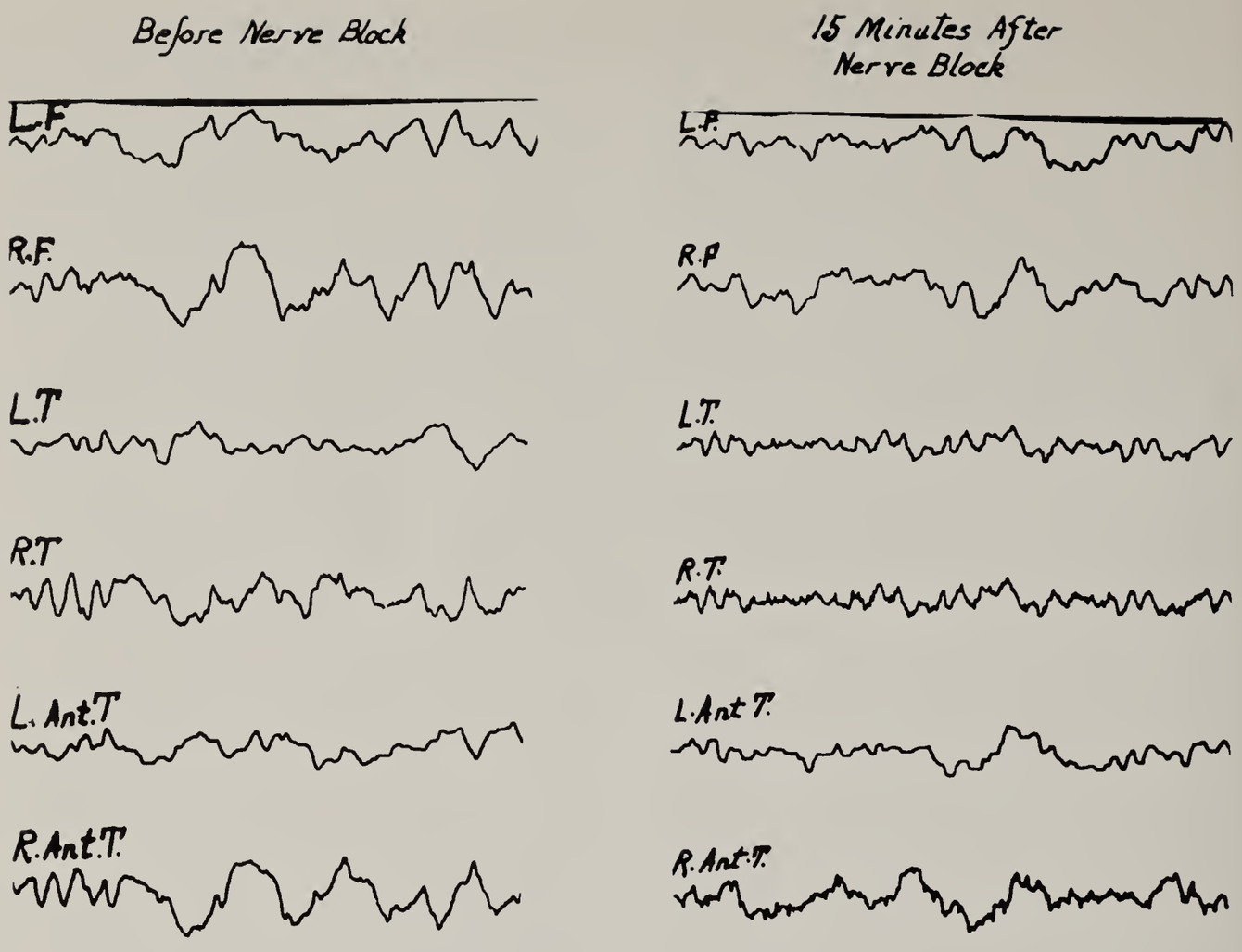


Fig. 1—Electroencephalogram of Percy D., age 76, eight hours after a left hemiparesis. *On the left:* the record shows wave focus of 1½ to 2 second frequency in the right temporal and bifrontal leads. Background activity about 7/sec. Impression: slow wave focus centering in the right fronto-temporal area. *On the right:* 15 minutes after stellate block with Horner's syndrome on the right. All slow activity decreased. Focus reduced and entire record looks more normal. Impression: tracing greatly improved.

tion, diuretics nor dextran has proven value; they may even be harmful.[15]

ANGINA PECTORIS

Sympathetic blocks for angina pectoris were undertaken primarily to interrupt sensory afferent impulses, and I well remember a rather obese club manager with severe angina running up the steep stairway of the lecture hall after a bilateral dorsal sympathectomy. He had no chest pain but was dyspneic so that the danger signal of undue exertion was not destroyed. We had also employed at one time stellate blocks in pulmonary embolism on the assumption that certain autonomic reflexes mediated through sensory receptors and parasympathetic efferents added to the morbidity and mortality of this vascular accident.[17] But later, in doing subtotal sympathectomies for hypertension (to be discussed below), it became obvious that the removal of the upper thoracic ganglia inhibited the tachycardia and rise in blood pressure which follows exercise. This, of course, is one of the simple clinical criteria which cardiologists use today in evaluating the beta-blocking action of propranolol or alprenolol on exercise tolerance.[18] In situations which increase adrenergic activity, myocardial oxygen demand and myocardial contractibility are reduced after sympathetic blockade.

Thus, an efferent adrenergic stimulation to the heart is also blocked and this

may not be beneficial to a failing heart but explains the present popularity of beta blockers in the hands of those who decried the use of nerve blocks in angina. In fact, a number of reports indicate that propranolol therapy in angina pectoris may improve life expectancy.[19] In heart transplants an obviously denervated heart seems to respond to many stimuli with acceleration and increased contractility.[20]

One area which has only recently been emphasized by George Burch is causalgia of the heart.[21] I shall discuss the problem of pain localized to the diseased or even surgically removed phantom responding in its early inception to sympathectomy.

The present emphasis on the intense treatment of cardiac arrythmias decreases mortality in the early phases of myocardial infarction. The place of intravenous lidocaine in the treatment of ventricular arrythmias is well established and intramuscular administration is also feasible. Lidocaine also acts on the completely denervated transplanted heart, but its use has superseded regional nerve blocks in cases of cardiac arrythmia in pulmonary embolism.[22]

Perhaps the most direct approach to the study of sympathetic innervation of the heart is the comparison of exercise electrocardiograms before and after stellate block (Fig. 2). We have done such tests with the late G. K. Fenn in the mid-forties; in the resting state little change was demonstrated, but after exercise of the blocked or sympathectomized patients, S-T depression was diminished together with a decrease in the severity of angina. Our observations were scant and never published. Wiener and Cox,[23] however, have presented a clear-cut report with such findings in 1966. The classic studies of Edwin Hirsch,[24] whose work it was a privilege to follow at Chicago's old St. Luke's Hospital, left no doubts about the rich innervation of the heart including the conducting system by autonomic fibers.

Obviously, then, in emergency situations requiring interruption of adrenergic stimuli, intravenous or intramuscular drugs are easier to administer than a stellate block. With the advent of direct revascularization procedures, the ischemic heart certainly can be more potently perfused than by release of vasoconstriction or dampening of O_2 demand. But I need to emphasize that sympathetic interruption not only severs the sensory afferents but blocks both alpha and beta receptors and may contribute to the faster development of collateral circulation by decreasing vascular resistance. Its addition to an aorto-coronary shunt or a Vineberg procedure may be well worth considering in the presence of extensive three-vessel involvement with high terminal resistance. The recent use of beta blockers in dissecting aneurysms of the thoracic aorta is reminiscent of the times when paravertebral alcohol blocks were used to alleviate pain. In some patients the dissection stopped, as in Myron Wheat's series treated with beta blockers and reserpine.

PANCREATIC PAIN

Excluding patients suffering from intractable pain due to carcinoma of the pancreas, our patients subjected to bilateral splanchnicotomy for calcareous pancreatitis showed an excellent response.[25] We believed that it would assume a standard place in the treatment of chronic sclerosing or calcareous pancreatitis accompanied by intractable pain. While this was a sensory denervation, other more direct methods of partial pancreatectomy and pancreaticojejunostomy have since been widely practiced. Also selective splanchnic angiography[26] helps to differentiate benign sclerosing lesions from carcinoma of the pancreas, where pain relief can be only temporary.

Recently I saw a patient with intractable pain due to calcareous pancreatitis who has had a pancreaticojejunostomy and biliary drainage; she was emaciated and addicted to narcotics. A splanchnic block with 5 percent phenol

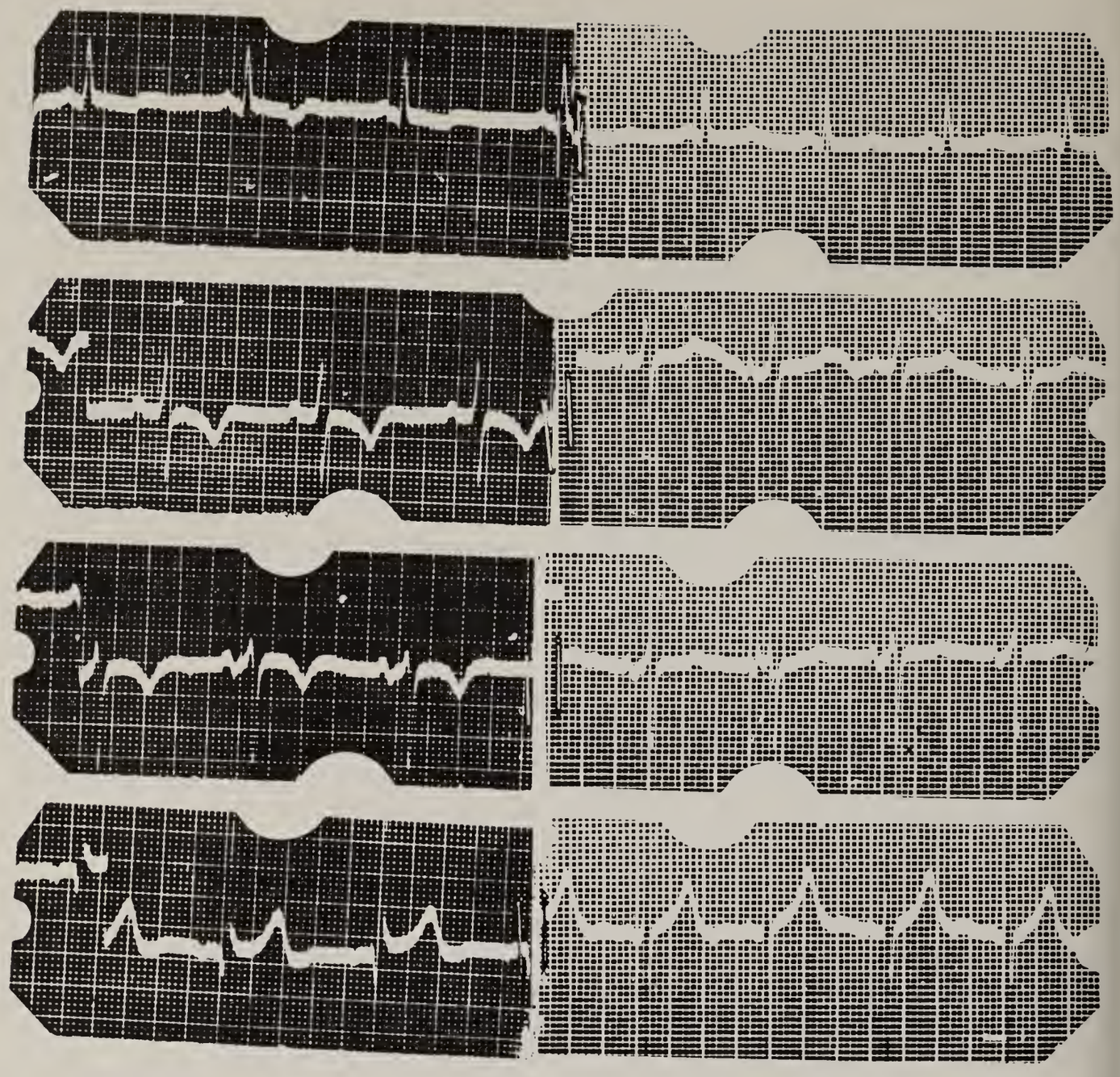


Fig. 2—Electrocardiogram of Pierce K. On the left are tracings before; on the right, tracings 15 minutes after bilateral stellate block. The control tracing shows deep inversion of T waves in leads II and III, and ST junction elevation in IV. After stellate block there is marked improvement of these ischemic changes.

performed by Dr. Max Sadove* permitted complete withdrawal of narcotics and gain in weight. In many debilitated patients phenol block can substitute for sympathectomy,[27] although a regeneration of fibers may follow. Reid of Glasgow, the principal exponent of this method has used it in more than 2,000 patients who showed comparable benefits to those that follow surgical removal, and with only one death.[28]

*Dr. Max Sadove, Chairman of the Department of Anesthesia at Rush-Presbyterian-St. Luke's Medical Center, has performed many of the nerve blocks at this institution, at the University of Illinois and at Hines veterans' facility. His enthusiasm, skill and cooperation are gratefully acknowledged.

DIABETES

In the early thirties, my co-workers and I were actively engaged in trying to evaluate the effect of celiac ganglionectomy, adrenal denervation or splanchnic

nerve section on the sugar tolerance of the experimental animal, and later on selected juvenile, insulin-resistant diabetic patients.[29] Of all the types of nerve sections, celiac ganglionectomy seemed to produce the greatest rise in tolerance —in some dogs as much as 3.83 grams per kilogram of body weight per hour from a basal state of 1 to 1.5 grams per hour. This meant that a 15-kg. dog would utilize 51 grams instead of 30 grams given intravenously.

It had been known to physiologists that both adrenal denervation and splanchnicectomy produced insulin-sensitivity in the experimental animal. We confirmed this in a number of publications and then tried splanchnicectomy on three juvenile diabetics. The operation was based on the assumption that glycogen mobilization from the liver would be inhibited and that the adrenal response to hyperglycemia would be controlled.

Out of three clinical cases published, the insulin requirement dropped in one patient from 55 to five units.[30] After a strenuous summer on a farm this patient showed a reactivation of his pulmonary tuberculosis and died within a year of the operation, still maintaining his tolerance.

In addition to the increase of insulin-sensitivity one might consider an inhibitory effect of sympathetic discharge on pancreatic release of insulin. When epinephrine was infused into normal subjects, despite the presence of marked hyperglycemia, immunoreactive insulin remained at basal levels until the infusion was stopped.[31]

I have recounted these early experiences not with the idea of advocating splanchnicectomy for insulin-resistant juvenile diabetes. But it is interesting that, in addition to epinephrine and norepinephrine, monoamines, notably serotonin, have been shown to inhibit insulin release from the beta cell. A serotonin blocker, methysergide maleate, increased secretion of insulin in diabetic patients.[32] Perhaps we need to seek drugs which release the inhibition of insulin on a neuroeffector basis.

HYPERTENSION

In a series of papers[7] we have reported on our indications for and results with splanchnicectomy for essential (primary) hypertension. Present day evidence still favors the multifactorial hypothesis of Pickering,[33] who regards blood pressure as a graded, quantitative characteristic, like weight and stature, caused by the summation of multiple inherited and environmental factors. Even in the younger age group, between 12 and 40 years of age, where secondary hypertension is supposed to have a high incidence, only one-third of a group of 229 cases were found to have secondary hypertension.[34] It is a vast community problem today, affecting over 20,000,000 people in this country.[35]

While opponents of splanchnicectomy for hypertension have always denied an increase of sympathetic tone in patients afflicted with essential hypertension, an examination of present day medical management indicates a plethora of drugs inhibiting catecholamine release, blocking alpha and beta receptors and decreasing blood volume. The use of diuretics, which is the first step in the medical management of essential hypertension, is especially intriguing because of the effect of splanchnicectomy on sodium diuresis.

I have described a water tolerance in hypertensives[36] and found, as have many others, that sympathetic efferent blockade to the kidney results in natriuresis by decreasing tubular reabsorption of sodium. Aside fron animal experiments recently summarized by Schrier and deWardener[37] which show clear-cut evidence of natriuresis in the acutely denervated kidney, the most convincing evidence is that of Wagner,[38] who found that subjects with autonomic insufficiency exhibit an exaggerated natriuretic response to infusion of saline solution when administered in the upright position. In addition, Gill and his associates[39]

reduced sympathetic tone with guanethidine and found an exaggerated natriuretic response to a restricted sodium intake. A decrease in renal vascular resistance and filtration fraction may alter both peritubular hydrostatic and oncotic pressure to explain the changes in sodium reabsorption.

The administration of propranolol, a beta-adrenergic blocking agent, also changes the pattern of sodium excretion both in normal man and in patients with heart failure.[40] The drug depresses cardiac output and has little if any effect on peripheral vasculature. Decreased sodium excretion is the result.

Obviously, there is a vast difference between an isolated autonomic blockade of the kidney and decrease in total vascular resistance which develops on administration of ganglioplegic vasodilators. Equally significant is the finding that the cardiovascular response to hemorrhage is mediated not only by the autonomic nervous system but by an angiotensin mechanism which acts through the medulla and the area postrema.[41] The central action of angiotensin is thus likely to be important in chronic renal hypertension. This may be the mechanism whereby the so-called neurogenic component of chronic renal hypertension is maintained, which Eric Ogden reported in 1940.[42]

Thus both the autonomic nervous system, notably the sympathetic efferents and the renin-angiotensin system are closely interrelated. The generation of angiotensin is under reflex control while angiotensin itself has autonomic effects at various sites.[43]

What I am driving at is that the vicious circle in hypertension can be broken among other sites at the renal-adrenal level. Even if the hypertension is obviously of renal origin as in post-toxemic hypertension or chronic pyelonephritis, sympathetic denervation not only diminishes peripheral vascular resistance, but affects the generation and the central neurogenic effects of angiotensin. Curiously enough, as a cry in the wilderness, Fowler and I reported[44] excellent results after splanchnicectomy in certain cases of renal hypertension.

What then are the "present day" indications for splanchnicectomy for hypertension and how extensive should the operation be?

I last reviewed this subject in 1962. With the present armamentarium of hypotensive drugs, the drug-resistant, progressively increasing hypertensive whose diastolic pressure is rising or, as Sir George Pickering pointed out,[33] who does not have the intelligence or morale to remain on permanent hypotensive medication, can be readily subjected to a one-stage subdiaphragmatic splanchnicectomy. This operation denervates the kidneys, the adrenals and the lower extremities, producing little if any postural hypotension. Small amounts of diuretics or adrenergic blockers can obviously be added postoperatively. Out of a total of 600, over 100 patients followed from 10 to 20 years and reported on in 1958,[7] showed conclusively that the results to be obtained depended on a severity index, an index of cerebral, cardiac and renal functions, and the state of eyegrounds.*

Subdiaphragmatic, supradiaphragmatic, thoracolumbar, and total sympathectomies have all had their advocates, and our group performed all of them at various times or for various indications. It gradually dawned on me that a simple one-stage bilateral splanchnicectomy and dorsolumbar sympathectomy does all that one can expect from denervating the target organs of kidney, adrenal, and abdominal viscera. It eliminates the vasomotor tone of the lower extremities. It will thus produce a mod-

*Only recently Laragh and his associates demonstrated that propranolol is uniformly effective in renin-dependent hypertension, whether malignant, renovascular, or essential. (New Eng J Med 287:1209-1214, Dec 14, 1972). Thus, this beta-blocker could become a preoperative test for sympathectomy.

erate postural hypotension in man, the erect animal, not sufficient to produce the severe disability of total sympathectomy.

The operation will dampen the pressor response to various stimuli which mobilize epinephrine and norepinephrine, although a basal secretion of catecholamines remains. Sympathetic denervation of the lower extremities decreases the secretion at and storage of catecholamines from sympathetic nerve endings in this area.

In twenty-seven patients with primary hypertension, the plasma catecholamine levels were significantly higher than in controls.[46] This may reflect increased sympathetic tone which we used to measure with the cold pressor test.

The disadvantage of inhibiting all vasopressor responses by total sympathectomy or adequate pharmacologic means is that it produces insufficient blood flow, particularly to ischemic organs and inhibits natriuresis by insufficient renal flow. Some of the drugs even decrease cardiac output, and so does sympathetic denervation of the heart. Thus selective adrenal and renal denervation is far preferable in cases of operable diastolic hypertension.

To illustrate the course of events when vasodilator drugs are prescribed in the presence of regional ischemia, the observations of Gillespie[47] are pertinent. We, too, have repeatedly observed a drop in skin temperature of an ischemic toe when general vasodilation was produced in non-affected areas.

This principle of hematometakinesia was clearly defined by Ochsner and deBakey in 1947.[48] It has significance in predicting increasing ischemia, nay, gangrene after lumbar sympathectomy for terminal vascular disease. This paradoxical gangrene described by me in 1944[49] after sympathectomy is still unrecognized by more recent workers in this field who have never seen it.[50] When the terminal vascular bed is severely damaged, the arteriovenous shunts and the more proximal, better vascularized areas drain away the already diminished arterial inflow, and acceleration of gangrene can result. To foretell such an event, all one has to do is to block the posterior tibial nerve at the ankle with procaine or xylocaine and take skin temperatures at the plantar surface of the big toe. If the rise in skin temperature is absent or amounts to only one or two degrees centigrade, sympathectomy will not improve the circulation of that area. I have observed increasing pallor or decrease in toe temperature, especially in patients with small-vessel disease or frostbite, and in such cases sympathectomy can be combined with toe amputation for faster rehabilitation of the patient. This "steal" is also recognized in the brain.[15]

Thus, to summarize my present attitude toward sympathectomy for hypertension, drug-resistant patients with fair renal function are suitable for limited splanchnicectomy. In the progressive malignant or premalignant type of hypertension with at least 15 percent of phenolsulfonephalein (P.S.P.) excretion in 15 minutes the operation is still worthwhile.

With these indications, a follow-up of patients from 10 to 22 years showed an improvement in 61 percent, progression in 24 percent and death in 20 percent. Since this is a group of selected severity these results were encouraging.[7]

Since this report in 1958, longer follow-ups are available. Although anecdotal experience is odious to some, I present the following brief history through the courtesy of Carl Hedblom, Jr., the patient's attending physician.

This 38-year-old diningcar steward first presented himself with average blood pressures of 230/130 mm.Hg, papilledema, retinal hemorrhages, a 58-percent cardiothoracic ratio, angina with abnormal cardiogram, and a 15-minute P.S.P. excretion of 20 percent. His severity index was thus 12, with a maximum severity of 17, which represents heart failure, renal function below 15 percent, diastolic pressure over 140 mm Hg, and papilledema.[7] Postoperatively, he was placed on chlorothiazide and guanethidine, later a monoamineoxidase inhibitor, all of which medication he had

received before operation. On his last follow-up in 1970, thirty years after splanchnicectomy, his blood pressure was 120/80, 110/70, and 90/60 mm. of Hg in the horizontal, sitting, and standing positions. He had reached retirement age and was employed as a janitor.

The point I wish to reemphasize is that the majority of moderately severe hypertensives are in no need of surgery. Nor is the malignant hypertensive in impending renal failure operable. But there is a well-defined small group in whom the operative mortality has been below two percent and the survival rate favorable. Besides, the over medicated hypertensive is suffering not only from his disease but from the effects of a total sympathectomy, which adversely affects his blood volume and sodium excretion.

SYMPATHECTOMY FOR PERIPHERAL VASCULAR SCLEROSIS

Nowhere has there been more confusion and argument than in this area. Some early authors glibly spoke of interruption of vasospasm, although obviously all that is accomplished is a decrease in peripheral vascular resistance and this mostly in the cutaneous area. Hand and foot, however, have very little musculature and chronic digital ulcers do heal in spite of a greatly diminished arterial inflow. At present the indications for sympathectomy in arterial occlusions, as recently summarized from our institution,[50] are as follows: Lumbar sympathectomy is added to restorative operations (1) when aorto-iliac reconstruction is planned only to bring increased flow to the profunda because of a closed superficial femoral artery, (2) in femoropopliteal restorations in which there is disease of the popliteal, (3) in addition to any direct surgical procedure in a patient who exhibits increased vasomotor tone or sudomotor activity.

Sympathectomy is the sole procedure under the following circumstances:

(1) Where the single symptom is claudication and an extensive distribution of lesions exists, and
(2) where there is concentration of vascular lesions in peripheral, especially digital, vessels with relatively mild disease in the vessels of the calf and thigh.

When chronic ischemia or diabetes have produced peripheral neuropathy with loss of ankle reflexes and vibration sense, the sympathetic outflow is already interrupted. The foot or hand is warm and dry. The disease has produced the sympathectomy, and a peripheral nerve block will not produce a rise in skin temperature. In such a situation, sympathectomy is futile and contraindicated.

There are other considerations in sympathectomies for the extremities. Clotting of the anastomosis will be less likely if decreased peripheral resistance accelerates blood flow through the anastomotic area; sympathetic vasoconstriction and discharge of epinephrine activates the Hageman factor which starts the chain reaction of coagulation;[51] spontaneous fibrinolysis may thus proceed more readily in an area whose sympathetics are blocked; if postoperative thrombosis complicates a by-pass procedure or a thromboendarterectomy, the reflex spasm will be inhibited.

In the early years of direct reconstructive surgery of arteries, many authors prided themselves for not adding "needless" surgery to the procedure and also for "being more scientific" by evaluating the results of these procedures without the benefit of sympathectomy. Today these procedures are well standardized, their advantages and limitations well known;[50] adding a lumbar sympathectomy to the direct procedure is another safeguard. When sympathectomies are performed as an emergency after the anastomosis clotted and clotting has extended, the end results are demonstrably poorer.

Most authors are positive that sympathectomy is useless for improving intermittent claudication.[50] There is a

situation, however, in which claudication can be relieved or greatly improved by sympathectomy. This is the case of a male, sedentary worker or executive in his early fifties with a short superficial femoral occlusion at the adductor canal with good collateral circulation in the angiogram. He has a cold, pulseless foot and is tense and hyperhydrotic. He claudicates on fast walking after one block. The other lower extremity is warm with well maintained pedal pulses. He has no diabetes or gout but may be intermittently hypertensive. He smokes one to two packages of cigarettes a day and was told to use alcohol to dilate his vessels, a suggestion which he conscientiously follows.

After a lumbar sympathectomy his foot gets warm and dry and his claudication distance gradually improves to six to eight blocks. He adheres to a low cholesterol diet, keeps his weight down, stops smoking and walks regularly increasing distances. Such a man, twenty years later, now in his seventies, has a warm, dry, pulseless foot, can play 18 holes of golf without discomfort. His weight is stable and right for his height and build. The opposite foot is now cold, pulseless with diminished oscillations. He is forgetful, irritable and his cardiogram shows some myocardial damage.

What alternate procedures could he have followed? He could have had no operation, but watched his weight, his diet and stopped smoking. The important thing is, however, that he cannot improve his walking ability by systematic walking at a slow pace. Sympathectomy has a sensory component, to be discussed under the head of causalgic states, which gives him just enough relief to start walking often and for longer periods of time. He can bear weight on the sympathectomized foot.

Or he could have had an easy femoropopliteal by-pass with an excellent immediate result, although there are early failures. If in ten or twenty years the by-pass fails, he is suddenly left with little or no collateral circulation. The failure rate after ten years is about 35 percent, and this is too high for this situation.[50]

This philosophy, of course, does not hold for the more advanced and diffuse occlusions. The aorto-iliac segments can be readily reopened or bypassed by a bifurcation graft, and as long as the profunda femoris is open, the patient will have an excellent result with an added sympathectomy. The short superficial femoral occlusion is bound to progress at an unpredictable rate and the disease is really a medical problem. The control of weight, diet and the abstinence from smoking should start preoperatively by subconscious propaganda. Never is a patient more susceptible to suggestion and medical orders than in this period.

However, as particularly emphasized by Humphries,[51] a sudden or gradual worsening or arterial occlusion cannot be foreseen; it occurs in unoperated or by-passed segments at about the rate of 31 percent over a four-year period. But in my experience with lumbar sympathectomies over a thirty-year period, acute occlusion of functioning collaterals or extension of atheromatous disease is very rare in the sympathectomized extremity unless it is injured.

The most important effect of lumbar sympathectomy on claudication is the fact that the foot becomes warm, less sensitive to cold and weightbearing, permitting the patient a graded daily exercise. The sensory nerve endings of the foot are less hypoxemic and the relief from this minor causalgia is what permits increased ambulation, and thus increased collateral circulation.

In a previous article,[52] I quoted the cases of a mailman and bankmessenger who had to walk to make a living and whose claudication disappeared several months after sympathectomy. In addition, a number of widely advertised vasodilators did not increase the exercise hyperemia registered by an electromyogram.[53] This method is far superior than subtle methods of isotope scanning or plethysmogram, because A-V shunting due to disease, vasospasm or pain interferes with results of the latter methods.

SYMPATHECTOMY FOR FROSTBITE

The results of sympathectomy for the late sequelae of frostbite consisting of hyperhydrosis, sensitivity to cold, Raynaud's phenomena, and continuous or intermittent burning pain are excellent and need no argument. Greatly debated in the past was the operation in the acute phase within a few days after the initial exposure. One experience with a curiously symmetrical frostbite occurring in a young inebriated woman lying in the snow for several hours permitted me to study the effects of sympathectomy on one side, leaving the other for control.[4] All ten toes were gangrenous to start with. On the operated side, the dorsal edema disappeared, the toes mummified and demarcation from viable tissue was complete in one week. On the non-operated side this demarcation took six weeks and the midmetatarsal amputation healed slowly. Neuritic and vasomotor phenomena developed only in the control limb.

Since this "anecdotal" experience I have been a strong advocate of emergency sympathectomy in case of severe, deep frostbite with irreversible damage even though in certain sessions of the National Research Council there was much opposition. A more recent report[54] leaves no doubt that early sympathectomy for certain types of frostbite is worthwhile.

SYMPATHECTOMY OF THE UPPER EXTREMITY

Contrary to lumbar sympathectomy done overwhelmingly for vascular sclerosis, sympathectomy for the upper extremity is usually done for Raynaud's phenomena, hyperhydrosis and small vessel disease. Most authors have felt that the operation is often incomplete in that regeneration and sprouting of sympathetic efferents make a permanent upper extremity denervation almost impossible.

This is not the place to enter into discussion of anatomic variation, the difference between pre- and post-ganglionic denervation, and the principle of sprouting in contrast to regeneration.[50] The fact of the matter is that in 1940 I reported 16 upper extremity sympathectomies in which the intermediate and inferior cervical ganglia were removed in addition to the first three dorsal ganglia.[55] For many reasons, not the least important being the medico-legal spectre of Horner's syndrome, we followed the crowd using a supraclavicular dorsal and, in the last 20 years, an axillary transthoracic approach leaving the stellate ganglion intact. A recent paper of Robert Goetz shows conclusively why this was a mistake.[50] His transaxillary approach through which the stellate ganglion is readily removed, undoubtedly provides a full and lasting sympathetic denervation, one of which lasted 31 years.

Since Raynaud's phenomena are infrequently due to central neurogenic impulses,[9] the majority of them are caused by digital arterial disease, collagen disease or frostbite. Great care must be exerted to eliminate the group of collagen diseases from sympathectomy. Full blown scleroderma, in our experience, may put up its ugly head 20 to 30 years after the premonitory appearance of Raynaud's phenomena. When these findings were recorded, the Mayo Clinic's criteria for primary Raynaud's disease had to be revised, which, after some delay, has now been acknowledged.

It is true, however, that scleroderma is perhaps a disease of capillaries with myxomatous subintimal deposits, and the collagen disease might well be secondary to this.[56] Even the pulmonary hypertension seen in Raynaud's phenomena may be due to increased pulmonary vascular resistance and not primarily to pulmonary fibrosis. Upper thoracic sympathec-

tomy could relieve this hypertension if pulmonary artery pressure can be shown to drop after upper dorsal paravertebral block.

Our experience with denervating the two upper extremities for hyperhydrosis continues to be excellent. Naturally, only severe cases, causing true handicap and inability to work are being considered. All four extremities should not be operated on because of the excessive postoperative sweating at the waist and other non-denervated areas.

In small vessel disease, such as occurs after frostbite, thromboangiitis obliterans or other forms of arteritis, sympathectomy heals ulcers, eliminates cold sensitivity and relieves pain.

Causalgic states have been discussed repeatedly by our group.[10] Sympathectomy is almost specific for true causalgia; but, reading some of the writings of our colleagues, one wonders about their exact indications. There is no real evidence that sympathetics carry pain fibers in the extremities. As pointed out by Ragnar Granit,[58] a demyelinated sensory fiber will conduct an electric discharge from an intact sympathetic fiber. In other words, the causalgic pain ensues when an efferent sympathetic discharge stimulates a naked, demyelinated sensory fiber. Demyelinization occurs in trauma, stretch, pressure or disease of a large somatic nerve, such as the median or sciatic, as in major causalgia, or the cross action may occur at smaller nerves or nerve endings, as in the minor causalgias or sympathetic dystrophies. In phantom limbs, breasts or penis, to mention just a few of the organs whose loss has caused severe pain in a non-existing area, it is most likely that the stimulus for pain projected into an amputated or diseased area, originates in the cross-section of an afferent sensory pathway, activated by efferent, sympathetic stimulation. This is the reason why sympathetic blockade or sympathectomy abolish the pain—provided it is not permitted to persist too long.

In 1945 I presented a diagram[59] to indicate how the continuous barrage of sensory impulses affects spinal cord and later cerebral cell stations, thus establishing the concept of three sensory neurons.

When pain is clearly abolished on sympathetic blockade with xylocaine but not after a sham injection of physiologic saline solution, sympathectomy is eminently successful, but it must be quite extensive, D_{10} to L_4, for the lower extremity, inferior cervical ganglion to D_4 for the upper extremity; if pain is unrelieved, but spinal anesthesia relieves it, a second neuron is involved. I have seen intractable pain persist in totally anesthetized areas; in such cases only a central type of operation or a frontal lobotomy can help. These are the badly neglected cases, and psychiatric help in my experience has not been successful.

Sympatheticolytic drugs cannot be given in sufficient doses, although intra-arterial reserpine can relieve symptoms for a few hours. Unquestionably, the so-called cardiac neurosis in patients with known myocardial disease is on such a basis.[21]

The failure of sympathectomy in causalgic states is thus due either to incomplete denervation or to a late phase of the disease in which this operation cannot help. Therefore, a study of the pain pathways is mandatory.

DISCUSSION

Certain basic principles emerge from this survey of past experience. Sympathectomy can produce lasting denervation, provided its extent is carefully planned. Sympathectomy will result in a regain of vascular tone, but the vasculature does remain free of central or reflex impulses; it will inhibit sudden fluctuations and provide for a more even basal flow. The sympathetics carry afferent, pain-conducting fibers from the viscera including heart and kidney, but such fibers in the extremities do not seem to exist. It is

true, however, that a damaged, demyelinated sensory nerve, nerve-ending or neuroma can be cross-stimulated by intact efferent sympathetic fibers. Whether this occurs in the ischemic foot, as has been suggested by J. C. Owens,[50] remains to be shown. Most importantly, regional sympathetic denervation, as accomplished by sympathectomy, is superior to the so-called pharmacologic sympathectomy, which not only has to be pushed to the point of intolerance but introduces the disabling effect of total sympathectomy. This produces not only postural hypotension, but may produce disabling natriuresis and drain blood from ischemic areas because of hypotension, hypovolemia, and decrease in cardiac output.

Finally, when beta-receptors are blocked without inhibiting alpha-receptors, the latter will mediate vasoconstriction.[60]

Obviously, a pharmacologic block is temporary, non-invasive and certainly simpler for the patient than a surgical removal; when the sympathetic block is desired to be long-lasting, the tyranny of long-term drug administration with its possible side effects suggests a surgical approach.

REFERENCES

1. deTakats G, Beck WC, Roth E: The neurocirculatory clinic. A summary of its activities. Ann Int Med **13**:957-979 (Dec), 1939

2. Leriche R: Physiologie pathologique et traitement chirurgicale des maladies arterielles de la vasomotricité. Masson et Cie Paris, 1945

3. Gilbert NC deTakats G: The emergency treatment of apoplexy. JAMA **136**:659-669 (March 6), 1948

4. deTakats G: Vascular Surgery. Philadelphia and London, WB Saunders Co, 1959

5. deTakats G, Walter LE, Lasner J: Splanchnic nerve section for pancreatic pain. Ann Surg **131**:44-57 (Jan), 1950

6. deTakats G, Fenn GK, Trump RA: Splanchnic nerve section in juvenile diabetes. I. Selection of cases for operation. Ann Int Med **7**:1201-1216, 1934

7. deTakats G, McDonald GO, Harridge WM: The vicious circle in hypertension. Surgery **43**: 113-124 (Jan) 1958

8. deTakats G, Fowler EF, Jordan P, Risley TL: Sympathectomy in the treatment of peripheral vascular sclerosis. JAMA **131**:495-499 (June 8), 1946

9. deTakats G, Fowler EF: Raynaud's Phenomenon. JAMA **179**:1-6 (Jan 6), 1962

10. deTakats G: Sympathetic reflex dystrophy. Med Clin N Amer **49**:117-129 (Jan), 1965

11. deTakats G: The controversial use of cervical sympathetic block for apoplexy. Ann Int Med **41**:1196-1210 (Dec), 1959. Surgery **38**:915-927 (Nov), 1955

12. Aring CD: Cerebral Vascular Accident in Current Therapy. Philadelphia, WB Saunders Co, 1954, p. 665

13. Harmel MH, Hafkenshiel JM, Austin GH, Crumpton CW, Kety SS: The effect by bilateral stellate ganglion block on the cerebral circulation in normotensive and hypertensive individuals. J Clin Invest **28**:415, 1949

14. Lassen NA: The luxury perfusion syndrome and its possible relation to acute metabolic acidosis. Lancet ii: 1113-1115 (Nov 19), 1966

15. Cerebral Blood Flow. Ed. by Brock M, Fieschi L, Ingvar DM, Lassen NA, Schurman K. Heidelberg-New York, Springer-Verlag, 1969

16. Meyer JS, Kanda T, Fukuyushi Y, Shimazu K, Dennis E, Ericsson AD: Clinical prognosis and hemispheric bloodflow in cerebral infarction. Stroke **2**:383-394 (Jul-Aug), 1971

17. deTakats G, Jesser JM: Pulmonary embolism: Suggestions for diagnosis, prevention and treatment. JAMA **119**:1415 (Apr 13), 1940

18. Sealey BJ, Libjedal J, Nyberg G, Ablad B: Acute effects of oral alprenol on exercise tolerance in patients with angina pectoris. Brit Heart J **33**:481-488 (Jul), 1971

19. Lambert DMD: Beta blockers and life expectancy in ischemic heart disease. Lancet **i**:793-794 (Apr 8), 1972

20. Kahn DR, Larr EA, Korsh MM: Long-term function after human heart transplantation. JAMA **218**:1699-1700 (Dec 13), 1971

21. Burch GE, Giles TD: Cardiac causalgia. Arch Int Med. **125**:809-814 (May), 1970

22. deTakats G: Pulmonary embolism. A second look. J Cardiac Surg Special Number, Vienna Congress, Sept, 1967

23. Wiener L, Cox JW: Influence of stellate ganglion block on angina pectoris and the post-exercise electrocardiogram Amer J Clin Sci **252**: 289-294 (Sept), 1966

24. Hirsch EF: The innervation of the vertebrate heart. Springfield, Illinois. Charles C Thomas, 1970

25. deTakats G, Walter LE, Lasner J: Splanchnic nerve section for pancreatic pain. Ann Surg **131**:44-57 (Jan), 1950

26. Boijsen E, Ehman LA, Lundh G: Selective splanchnic angiography. *In* Advances of Surgery **3**:13-73, Chicago, Year Book Medical Publishers, 1968

27. Haxton H: Chemical sympathectomy. Brit Med J **1**:1026-1031, 1949

28. Reid W: *In* Arterial Surgery. Ed. by Mackey WA, MacFarlane JA, Christian MS. Oxford, Pergamon Press, 1964

29. deTakats G, Cuthbert FP: Surgical attempts at increasing sugar tolerance. Arch Surg **26**:750-761 (May), 1933

30. deTakats G: Splanchnic nerve section in juvenile diabetes. Ann Surg **102**:22-29 (Jul), 1936

31. Porte D Jr, Graber AL, Kuzuga T, Williams RM: The effect of epinephrine on immunoreactive insulin levels in man. J Clin Invest **43**:228-236 (Feb), 1966

32. Quickel KE Jr, Feldman JM, Lebovitz ME: Enhancement of insulin secretion in adult onset diabetes by methysergide maleate. J Clin Endocr **33**:877-881 (Dec), 1971

33. Pickering GW: High Blood Pressure. New York, Grune & Stratton, Inc. Third Edition, 1970

34. Tudor MJ: Semicontinuous screening of a whole community for hypertension. Lancet **2**:223-226, 1970

35. Creditor MC. Schoenberger JA. Control of hypertension. An unmet challenge. Chicago Med Bull **75**:75-76 (Jan 29), 1972

36. deTakats G, Fowler EF: The water tolerance of the hypertensive patient. Its relation to operability. Am Heart J **38**:239-247 (Aug), 1949

37. Schrier RW, deWardener ME: Tubular reabsorption of sodium ion, influence of factors other than aldosterone and glomerular filtration rate. New Eng J Med **285**:1292-1303 (Second part) (Dec 2), 1971

38. Wagner HN Jr: The influence of autonomic vasoregulator reflexes on the rate of sodium and water excretion in man. J Clin Invest **36**:1319-1327, 1957

39. Gill JR Jr, Bartter FC: Adrenergic nervous system in sodium metabolism. II. Effects of guanethidine on the renal response to sodium deprivation in man. New Eng J Med **275**:1466-1471, 1966

40. Epstein SE, Braunwald E: The effect of adrenergic blockade on patterns of urinary sodium excretion: Studies in normal subjects and in patients with heart disease. Ann Int Med **65**:20-27, 1966

41. Katic F, Lavery M, Lowe RD, Joy MD, Scroop GD: Role of central effects of angiotension in response to haemorrhage in the dog. Lancet **ii**:1359-1356 (Dec 18), 1971

42. Ogden E, Brown LT, Page EW: The increased sensitivity of arterial muscle in the prehypertensive phase of experimental hypertension. Amer J Physiol **129**:560, 1940

43. Joy MD, Lowe RD: The site of cardiovascular action of angiotensin ii in the brain. Clin Sci **39**:327-336, 1970

44. deTakats G, Fowler EF: Surgical treatment of hypertension. III. Neurogenic versus renal hypertension from the standpoint of operability. Surgery **21**:773-799, 1947

45. deTakats G: Surgical physiology of hypertension. Surg Clin N Amer **42**:91-107 (Feb), 1962

46. DeQuattro V, Chan S: Raised plasma-catecholamines in some patients with primary hypertension. Lancet **i**:806-809 (Apr 15), 1972

47. Gillespie JA: The case against vasodilator drugs in occlusive vascular disease of the legs. Lancet **ii**:995, 1959

48. DeBakey ME, Burch GE, Ray T, Ochsner A: The borrowing-lending hemodynamic phenomenon (hematometakenesia) and its therapeutic application in peripheral vascular disturbances. Ann Surg **126**:850, 1947

49. deTakats G: The value of sympathectomy in the treatment of Buerger's disease. Surg Gynec Obstet **79**:359, 1944

50. Management of Arterial Occlusive Disease. Ed. by Dale A, Chicago, Year Book Medical Publishers, 1971

51. McKay DG, Latour JG, Parrish MH: Activation of Hageman factor by adrenergic stimulation. Thromb Diath Haemorrh **23**:417-422 (No. 3), 1970

52. deTakats G: The place of sympathectomy in the treatment of arterial occlusive disease. AMA Arch Surg **77**:655-676 (Nov), 1958

53. deTakats G: Intermittent claudication studied by electromyography. AMA Arch Surg **81**:94-102 (Jul), 1960

54. Shumacker HB Jr, Kelman JW: Sympathectomy in the management of frost bite. Arch Surg **89**:575, 1964

55. deTakats G: Analysis of results following sympathectomy for peripheral vascular disease. Amer J Surg **47**:78, 1940

56. Norton WC, Narda JM: Vascular disease in progressive systemic sclerosis (scleroderma). Ann Int Med **73**:317-329 (Aug), 1970

57. deTakats G: The surgical treatment of hyperhydrosis. AMA Arch Dermat **76**:31-38 (Jul), 1957

58. Granit R, Leksell L, Skoglund CR: Fiber interaction in injured or compressed region of nerve. Brain **67**:125, 1944

59. deTakats G: Causalgic states in peace and war. JAMA **128**:699-704 (Jul 7), 1945

60. Coupar IM: The effect of isoprenaline on adrenoreceptors in human saphenous vein. Brit J Pharmacol **39**:465-475, 1970

ABSTRACTS

OF PUBLICATIONS BY THE STAFF

Biochemistry

Harrison WH, Codd E, Gray RM: Aluminum inhibition of hexokinase. *Lancet 2:277, Aug. 5, 1972*

Aluminum ion was found to inhibit the hexokinase of various tissues of the guinea pig. At $1x10^{-4}M$ Al^{3+}, all tissues studied were inhibited, including heart (57 percent), kidney (79 percent), liver (100 percent), brain (66 percent), skin (100 percent), and spleen (37 percent). An aqueous extract of kidney, representing soluble hexokinase, was 30 percent inhibited at $1x10^{-4}M$ Al^{3+} and 11 percent inhibited at $1x10^{-5}M$. Our studies suggest that hexokinase and possibly all phosphate-transferring systems, including ATP and Mg^{2+} are possible biological target sites for Al^{3+}.

Harrison WH, Gray RM: Stimulation of yeast hexokinase by catecholamines and related compounds. *Arch Biochem Biophys 151:357-360, 1972*

Yeast hexokinase has been found to be qualitatively similar to brain hexokinase with respect to stimulation by catechol and catecholamine. As with the brain enzyme, significant stimulation occurs only when Mg^{2+} and H^+ concentrations are suboptimal and the concentration of the phosphate acceptor (glucose or 2-deoxyglucose) exceeds the half saturation level; the catechol group is required and the side-chain substituent alters the activity. Quantitatively, the two enzymes differ; for example, ten times as much Mg^{2+} is required to elicit maximal stimulation response with the yeast as with the brain enzyme. There are wide range differences in stimulation factors between different preparations which cannot be explained at present. As with the brain enzyme, catecholic compounds appear to be useful as test probes for enzyme mechanism studies, and the stimulation phenomenon may be significant with respect to hexokinase control mechanisms.

Scheving LE, Dunn JD, Pauly JE, Harrison WH: Daily variation in 5-hydroxytryptamine in rat spleen and the effect of stimuli on the rhythm. *Anat Rec 173:257-264, 1972*

Fluorometric measurements were made of 5-hydroxytryptamine levels in spleens obtained from separate subgroups of adult male rats killed at two-hourly intervals over four separate 24-hour time spans. For three weeks prior to obtaining tissue, all rats were standardized carefully and were subjected to 12 hours of light (0600-1800) followed by 12 hours of darkness. Analyses showed in each study very significant fluctuation over the 24-hour time scale; the range of change over this period was as great as 131 percent. The phasing of the rhythms, in spite of the rigid environmental synchronization, was not similar in any of the four studies. Possible explanations for this unexpected desynchronization are discussed. Spleen weights also fluctuated with a significant 24-hour circadian frequency.

In addition, the rhythm characterizing this amine was described in female rats as well as the effect of different stimuli on the same rhythm. These stimuli were ether, immobilization, and a "novelty" situation; and all three significantly increased the levels of 5-HT in spleen when the overall 24-hour mean values of each experimental group were compared with controls. However, in all cases there were discrete time points when significant differences in 5-HT levels could not be obtained with any of the stimuli. This study demonstrates that the effect of the stimuli used depends on the phase of the rat's circadian system during which it was applied. The necessity of considering the natural rhythmic fluctuation in any investigation evaluating this biogenic amine in spleen is demonstrated.

Cardiorespiratory Diseases

Lourenco RV, Loddenkemper R, Carton RW: Patterns of distribution and clearance of aerosols in patients with bronchiectasis. *Amer Rev Resp Dis 106:857, 1972*

Pulmonary distribution and clearance of inhaled aerosols were studied in 14 patients with bronchiectasis confirmed by bronchography. Abnormalities in the deposition of the particles were present in eight patients, who demonstrated a central deposition of particles in the lungs; such a pattern of deposition is abnormal for the size of particles and the pattern of breathing used during inhalation. These eight patients had more marked airway obstruction and more severe symptoms of chronic bronchitis. Fewer particles were deposited in areas with localized saccular bronchiectasis than in the contralateral nonbronchiectatic areas.

Abnormalities in clearance were apparent in all patients. They were characterized by abnormally slow clearance rates immediately after inhalation of the particles and by the presence in the photoscintigrams of juxtahilar areas of accumulation of particles. There were no significant differences between these patterns of clearance and those found in patients with bronchitis without bronchiectasis.

Endocrinology

Becker FO, Schwartz TB: Sympathetic blockade in hyperthyroidism, *Arch Intern Med 129:967-971, 1972*

Antithyroid drugs are commonly used in the treatment of hyperthyroidism. Toxic reactions to antithyroid drugs are infrequent but the management of such patients, in whom the use of radioactive iodine is not indicated, becomes a problem. Three cases are reported in which sympathetic blockade was followed by surgery. This newer approach appears to be a valuable adjunct in the treatment of those hyperthyroid patients with antithyroid drug toxic reaction in whom surgery seems to be the best alternative form of treatment.

Garland JT, Lottes ME, Kozak S, Daughaday WH: Stimulation of DNA synthesis in isolated chondrocytes by sulfation factor. *Endocrinology 90:1086, 1972*

Growth hormone dependent serum factors (*e.g.* sulfation factor or SF) regulate both proliferation of chondrocytes and formation of matrix. Previous work in this field has generally employed explants of rat cartilage. We have investigated the action of sulfation factor on isolated chick chondrocytes. Pelvic rudiments from 15-day chick embryos were treated with collagenase and trypsin to liberate chondrocytes. Chondrocytes were then isolated by differential centrifugation. Aliquots containing about 300,000 cells were pipetted for subsequent incubations. Normal human serum (NHS) added to the medium stimulated incorporation of [^{3}H]thymidine into the cold TCA ppt, as compared to serum from hypopituitary subjects. When a patient with low serum SF was treated with growth hormone the serum SF activity increased. In contrast, bovine growth hormone added *in vitro* did not have any significant effect, either alone or in the presence of 0.5 percent NHS. Pulse labeling after various periods of incubation demonstrated maximal stimulation of uptake at 31 hours. A graded response of thymidine incorporation was obtained with most NHS at concentrations of 0.6 to 6 percent of the final vol. Stimulation with 5 percent NHS was as great as 100-fold at 24 hours. In some NHS and most rat sera there appeared to be inhibitory factors. This inhibitory effect was decreased by heating at 56° for 30 min. The addition of phosphatidylcholine abolished some of this inhibition, suggesting that phospholipids may be a part of the SF receptor.

Therefore, the isolated chondrocyte preparation is a highly sensitive and responsive system for studying hormonal regulation. The addition of normal human serum in this system results in a remarkable stimulation of DNA synthesis. Delivery of identical populations of chondrocytes to over 100 incubation tubes has the potentiality of greatly facilitating study of SF action and providing a more convenient quantitative assay.

Riddle MC, Ryan WG, Schwartz TB: Human plasma free fatty acid concentration at rest and after norepinephrine infusion: Effect of preceding physical activity. *Metabolism 21:1063-1072, 1972*

Plasma free fatty acid concentrations before and after low-dose, short-term norepinephrine infusion (0.1 μg/kg/min for 5 min) have been studied in nine normal men under conditions of varying preceding physical activity. Free fatty acid responses to norepinephrine were greater under nonbasal conditions, whether morning or afternoon, than under morning-basal conditions. Pre-infusion base-line free fatty acid values were not similarly affected. It appears that preceding physical activity enhances adipose tissue sensitivity to catecholamines, and possibly also peripheral uptake of free fatty acids from circulation. These changes may account for some of the considerable variability in human plasma free fatty acid levels not readily explained by sympathetic nervous or insulin effects.

Northrop G, Ryan WG, Schwartz TB: Propranolol-induced insulin release in isolated rat islets of Langerhans. *In press.*

Isolated rat islets of Langerhans were incubated in media containing different concentrations of propranolol, glucose (3 mg/ml) and both propranolol and glucose. Immunoreactive insulin was measured in the medium following incubation. Pretreatment with 20 μgm/ml of propranolol prevented glucose-mediated insulin release. Propranolol alone in concentrations up to 25 μgm/ml did not cause insulin release; however at 50 μmg/ml this drug had strong beta-cytotrophic activity.

Infectious Diseases

Kallick CA, Levin S, Reddi KT, Landau WL: Systemic lupus erythematosus associated with haemobartonella-like organisms. *Nature-New Biol 236:145-146, 1972*

Haemobartonella organisms have been known to cause many animal dieases and are known to infect every animal species. An association between these agents and systemic lupus erythematosus (SLE) was observed. Blood films from eight patients with known SLE were compared with sixteen normal controls by graduate veterinary physicians looking for specific haemotrophic infections resembling animal infections of the haemobartonella group. Examination was by acridine orange and fluorescein conjugated specific-direct antibody obtained from animals with several kinds of haemotrophic infections. With acridine orange, all eight patients had suggestive erythrocyte structures which resembled haemobartonella agents. Two controls had similar structures. Using direct fluorescein conjugated antibodies, four of eight Lupus patients had suggestive structures on the erythrocytes which was stained with conjugated antibody Anaplasma marginale and Eperythrozoon suis. No controls had similar fluorescence.

These findings suggest that an association may exist between haemobartonella-like agents and systemic lupus erythematosus, and indicate further study.

Neurology

Davis FA: Impairment of repetitive impulse conduction in experimentally demyelinated and pressure-injured nerves. *J Neurol Neurosurg Psychiat 35:537-544, 1972*

Repetitive impulse conduction was studied in segmentally demyelinated periperhal nerves in guinea-pigs with experimental allergic neuritis (EAN) and in pressure-injured frog sciatic nerves. Normal guinea-pig sciatic-peroneal nerves maintained at 37° C conducted compound action potentials with only minor amplitude decreases at stimulus frequencies up to 200/sec. In contrast, nerves in EAN guinea pigs maintained at 37° C demonstrated a rapidly progressive decrease in action potential amplitude when stimulated as slowly as 10 to 25/sec. The decrease is greater the higher the frequency of stimulation. At 100 stimuli/sec all EAN preparations showed more than a 50 percent reduction in action potential amplitude. These effects are reversible. In pressure-injured frog sciatic nerves similar effects occurred at stimulus frequencies as low as 50/sec. Normal frog nerves conducted up to 200 impulses/sec with little amplitude decrease. The probable mechanism and clinical significance of these results are discussed.

Davis FA, Jacobson S: Altered thermal sensitivity in injured and demyelinated nerve. *J Neurol Neurosurg Psychiat 34:551-561, 1971*

Electrophysiological studies were performed on frog and guinea-pig peripheral nerves to determine the effect of temperature on conduction at the site of pressure and demyelinating lesions. An increased susceptibility to thermally-induced conduction blockade has been demonstrated. In pressure-injured frog and guinea-pig nerves, conduction blocks occur at temperatures approximately 6°C lower than in normal nerves. A similar phenomenon occurs in guinea-pig demyelinated nerve (experimental allergic neuritis) and in some cases at temperatures around 15°C lower than in controls. It is suggested that these effects are the result of a critical lowering by temperature of an already markedly depressed conduction safety factor. In support of this, it has been shown that calcium ion depletion, which would be expected to increase the conduction safety factor by lowering the threshold for excitation, counteracts the increased thermal sensitivity of frog pressure-injured nerve. These findings are discussed in relation to well-known temperature effects in multiple sclerosis. They add support to an earlier proposed hypothesis that the changes in signs and symptoms with a change of body temperature in multiple sclerosis may be caused by an effect of temperature on axonal conduction.

Obstetrics & Gynecology

Misenhimer HR: Examination of the recently delivered placenta by phase contrast microscopy. *Amer J Obstet Gynec 114:796-802, 1972*

Phase contrast microscopic examination of the recently delivered placenta offers a readily available method of identifying abnormalities of the chorionic villi. This type of examination on 995 placentas from both normal patients and those with a variety of clinical abnormalities showed a statistically significant increase in the incidence of syncytial, stromal, and combined abnormalities in patients with these clinical problems. The pathogenesis of these abnormalities remains to be defined.

Northrop G, Ditzler J, Ryan WG, Wilbanks GD: Estriol excretion profiles in narcotic-addicted pregnant women. *Amer J Obstet Gynec 112:704-712, 1972*

Estriol excretion patterns were studied in eight methadone-dependent pregnant women during their last trimester of gestation. In women maintained on narcotic drugs the concentration of estriol in their urine remained low. Following withdrawal of these patients from narcotic drugs their urinary estriol concentrations rapidly increased toward or exceeded the average values expected for their gestation time.

Neither ACTH nor Metopirone stimulated estriol excretion in these addicted pregnant women; however, a daily dose of four mg. of dexamethasone decreased urinary estriol excretion. It is concluded that careful consideration be given to the drugs a patient may be taking when fetal well-being is monitored with urinary estriol excretion.

Otolaryngology

Holinger P, Lutterbeck E, Bulger R: Xeroradiography of the larynx. *Ann Otol 81:806, 1972*

Xeroradiography provides edge enhancement x-ray type of examination through an electrical process not available through conventional radiography. All tissue densities are represented in a single image, eliminating the need for taking two films of different densities, while radiation exposure is the same. Xeroradiographs are made on aluminum plates with a selenium layer which is electrically charged rather than on photographic film. Selenium is a photoconductor, and a positive electric charge on its surface will remain for a long period of time until acted upon by light or x-rays. The selenium coated aluminum plate is enclosed in a cassette. It is exposed to an x-ray beam which produces positive and negative charges in the selenium surface in proportion to the x-rays as the selenium is discharged. The charge pattern remaining on the plate after exposure depicts the varying densities of the anatomic structures being examined, according to the amount of radiation absorbed. Development consists of blowing a cloud of negatively charged fine blue plastic powder over the positively charged plate. An image is thus formed producing a vertical electrical field component with enhanced borders and can be transferred to paper by electrostatics. When this technique is used for examining soft tissue of the neck it results in very excellent images with all densities of tissues recorded in detail and with great contrast. Differences in density are accentuated, especially the margins of soft tissues and calcifications, creating an impression reminiscent of a relief map. While soft tissue xerography of the breast is done with low voltage x-ray 24 to 30 KV, the very useful technique of xerography of the skull, neck, larynx and long bones uses higher voltages of between 120 and 125 KV.

Holinger P, Schild JA: Pharyngeal, laryngeal and tracheal injuries in the pediatric age group. *Ann Otol 81:538, 1972*

Trauma of the larynx and immediately adjacent anatomical structures of infants and children is divided into three age groups: infants 0 to 1½ years, children from 1½ years to 12 years, adolescents 13 to 18 years. Trauma in the first group is largely the result of impacted intralaryngeal foreign bodies, traumatic or prolonged tracheal intubation, and hypopharyngeal aspiration; in the second group foreign bodies and intubation play a lesser role while the activities of childhood (falls, misadventures in sports) become more prominent; automobile injuries increase with older children in this group while in adolescents, automobile-related

injuries far outweigh all others in incidence of etiology. Those in the first group were seen early in relation to the time of injury; in the other two groups, diagnosis was usually delayed, and therefore, definitive treatment could be instituted only late. The pathology of edema, stenoses, lacerations, fractures of cartilages, tracheal separations and trauma from cuff tubes was encountered. Treatment in the early age groups was conservative; in the older groups immediate repair or intralaryngeal splinting was done if seen early; if seen late, conservative measures such as occasional dilatation were employed in the prepuberty age levels; more active surgical reconstruction was utilized in the older adolescents, consisting of thyrotomy and resection of scar with skin grafting, or direct tracheal anastomoses, arytenoidectomy, or the use of a tantalum keel.

Pediatrics

Lubchenco LO, Searls DT, Brazie JV: Neonatal mortality rate: Relationship to birth weight and gestational age. *J Ped 81:814-822, 1972*

Data on neonatal mortality rates, by birth weight and gestational age, are presented in a variety of ways to indicate their usefulness in everyday practice. The conventional rates by birth weight groupings have been useful in the past, but data by both birth weight and gestational age are necessary for evaluation of current perinatal practices. Mortality rates in small blocks and in curvilinear zones by birth weight and gestational age are useful in evaluating the outcome of individual pregnancies and newborn infants. Each of these methods serves a specific need, and the advantages of each are described. The importance of using both birth weight and gestational age, when reporting mortality rates in neonatal populations, is emphasized.

Physiology

Scheving LE, Dunn JD, Pauly JE, Harrison WH: Circadian variation in rat serum 5-hydroxytryptamine and effects of stimuli on the rhythm. *Amer J Physiol 222:252-255, 1972*

Fluorometric measurements were made of 5-hydroxytryptamine levels in serum obtained from separate subgroups of adult male rats killed at two-hour intervals over three separate 24-hour spans. For three weeks prior to obtaining blood, all rats were standardized carefully and were subjected to 12 hours of light (0600-1800) followed by 12 hours of darkness. Analyses show that 5-hydroxytryptamine levels are highest during the last part of the light span and the first part of the dark span. The increase from the lowest to the highest two-hour mean value over a 24-hour period ranged from 23 to 33 percent in the three studies. A rhythm in 5-hydroxytryptamine levels also is demonstrated for female rats maintained on a schedule with light extending from 0400 to 1800. A study was made of the effect of three different experimental conditions on this rhythm in female rats: exposure to ether, to immobilization, and to a novelty situation. The ether and immobilization stimuli had a damping effect on the 5-hydroxytryptamine rhythm; the novelty had no effect. This damping of the rhythm in the two groups produced a statistically significant decrease in 5-hydroxytryptamine levels when compared to the controls at only a certain phase of the rat's circadian system. These studies demonstrate the importance of considering the circadian rhythms in any investigation evaluating this biogenic amine in serum.

SUGGESTIONS TO AUTHORS

Manuscripts. Manuscripts should be typewritten and double-spaced throughout, including tables, captions, references, etc. The title of the manuscript should be capitalized and begin at the normal lefthand margin of Page 1 and run across the entire page, with continuation on next line, if necessary. Authors should be listed in capital letters below title, one per line, with double-spacing between names. In footnotes on Page 1 please identify source (department) of article, and also authors as to staff and academic rank.

Figures should be drafted in black India Ink, and legends typed on a separate sheet in numerical order, using Arabic numbers. Glossy photographs are preferred to original charts. Medical drawings may be submitted in the original or glossy prints. Photographs and Figures should be lightly identified on back in pencil as to number and "Top," together with last name of author. Use Roman numerals to number Tables and include descriptive headings under number. Indicate in text where Figures and Tables should occur. Abbreviations preferred are: ml, kg, gm, mg, *u*g, mm, and mEq/1.

References. Number references serially in text, and list in numerical order beginning on a new page, in the following manner:

1. Gary GW, Bryan AC, Frayser R, Houston CS, Rennie IDB: Control of acute mountain sickness. Aerospace Med 42:81-84, 1971

List book references as follows:

2. Rafelson ME Jr, Brinkley SB, Hayashi JA: Basic Biochemistry. Third Edition. New York, Macmillan Company, 1971, pp. 96-208

Abbreviations of journals should correspond to those in the *Index Medicus.*

Reprints. One hundred reprints with identifying cover are supplied free of charge for each article published. Additional reprints are supplied at cost.

INCORPORATION OF AMINO ACIDS AND NUCLEIC ACID PRECURSORS BY CELL SUSPENSIONS ISOLATED FROM RAT LIVER

Patrick E. Lentz

ABSTRACT. The data in this report indicate that cell suspensions isolated by enzymatic digestion of rat liver retain the ability to incorporate labeled precursors into protein and RNA. The difference in sensitivity to actinomycin D may reflect a major physiological difference in the two major cell types. Detailed analysis of the types of RNA and the synthesis of various major classes of RNA by these cells in rodent liver is required to verify these differential responses.

INTRODUCTION

Mammalian liver is composed of at least five different cell types.[1] Hepatocytes or parenchymal cells constitute 90 to 95 percent of liver mass and 60 to 65 percent of the total cell number. Reticuloendothelial (littoral, von Kupffer, sinusoidal living) cells or liver macrophages constitute 5 to 10 percent of liver weight and 35 percent of the total cellular population. Bile duct, connective tissue and blood vessel wall cells represent a small percentage of the total cell number and a minor component of liver mass. The selective contributions of each cellular population to liver metabolism have not yet been examined, and parenchymal cells have been assumed to be largely responsible for the organ specific functions of liver. Several reliable techniques are now available for preparation of parenchymal and macrophage cells from rat and mouse liver,[2-7] and it is now possible to study the metabolism of discrete populations of liver cells free from the influences of other cell types, hormones or metabolites found in the intact liver or liver slices.

We have been interested in the rates of protein and nucleic acid synthesis in parenchymal and Kupffer cells. In the adult animal the liver maintains a high rate of protein synthesis,[8-10] producing in approximately equal amounts proteins for export and for replacement of its own substances. Incorporation of labeled amino acids into total protein and into specific proteins such as albumin, transferin, etc., *in vivo*, in perfused liver and in liver slices has conclusively established the cellular components essential for syn-

From the Section of Physiology, Department of Biomedical Engineering, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois and the Department of Physiology, Tulane University School of Medicine, New Orleans, Louisiana

Presented before the Department of Biomedical Engineering of Rush-Presbyterian-St. Luke's Medical Center, February 24, 1972

Supported in part by USPHS Institutional Research Support Grant and the Atomic Energy Commission

Patrick E. Lentz, Ph.D., Assistant Professor, Department of Physiology, Tulane University School of Medicine

thesis, intracellular transport and secretion of proteins.[10] However, the relative rates of synthesis and the types of proteins synthesized by hepatocytes and macrophages have not been elucidated. There are only a few studies which compare the incorporation of labeled precursors into proteins and nucleic acids by specific cells from rat liver. Ficq,[11] using autoradiographic techniques, demonstrated high rates of protein and nucleic acid synthesis in nuclei of liver parenchymal and macrophage cells. Ashley and Peters[12] have recently reported the sites of synthesis and migration of proteins in rat liver slices. Reticuloendothelial cell protein was labeled promptly and estimated to represent 5 percent of the total protein formed by liver. Shanmugan and Bhargava[13] and Jacob and Bhargava[14] have reported the incorporation of labeled amino acids and nucleic acid precursors into total protein and RNA by liver parenchymal cells prepared by mechanical means. Burton et al.[15] have found that parenchymal cells synthesized, *in vitro*, soluble fatty acid synthetase complex. Jezyk and Liberti[16] have demonstrated the incorporation of isoleucine and uridine into parenchymal cell protein and RNA. Casanello and Gerchenson[17] have recently reported successful culture of rat hepatocytes, and demonstrated that the metabolism of cultured cells as measured by the incorporation of ^{14}C-leucine into protein, oxidation of ^{14}C-glucose and induction of tyrosine alpha-ketoglutarate transaminase by dexamethasone could be maintained for at least thirty days.

The purposes of this study were: 1) to measure directly the incorporation of ^{14}C-leucine into total liver protein, liver macrophages and parenchymal cells *in vivo;* 2) to measure the *in vitro* incorporation of ^{14}C-leucine and ^{3}H-uridine into proteins and nucleic acids by cell suspensions isolated from rat liver; and 3) to compare the effects of actinomycin D, chloramphenicol and puromycin on the incorporation of labeled precursors into protein and nucleic acid of liver parenchymal cells and macrophages *in vitro*.

EXPERIMENTAL PROCEDURES

Materials

All radioactive compounds were obtained from New England Nuclear and used without further purification. The compounds were: ^{14}C-leucine, 260 mCi per μMole; ^{14}C-amino acid mixture, algal protein hydrolysate; ^{3}H-uridine, 28 Ci per μMole. Non-radioactive compounds and their sources were: collagenase, 125 units per mg from *Clostridium histolyticum*, Type IV; hyaluronidase, 370 units per mg, bovine testis, Type I; trypsin, 10,000 units per mg, bovine pancreas, Type I; deoxyribonuclease, 2400 units per mg, Type I; chloramphenicol; actinomycin D; and puromycin (all from Sigma); Hanks balanced salt solution 10 X (Difco Laboratories, Detroit, Michigan).

Experimental Animals

Male Charles River rats were maintained with free access to Purina Chow and water. Fed rats weighing 200 to 300 gm were used for preparation of hepatocytes and Kupffer cells from liver.

Preparation of Kupffer Cells and Hepatocytes

Kupffer cells were prepared as described previously.[7] Briefly, rat livers were perfused, chopped, incubated with 0.01 percent collagenase in glucose, potassium chloride, sodium chloride, pH 7.4 for two hours at 4°, and incubated with 0.005 percent trypsin for fifteen minutes at 37°. The heavy gelatinous matrix (ECM)[18] formed during the trypsin digestion, was dissolved by the addition of deoxyribonuclease, 240 units per cell pellet from 25 gm liver, and shaking for 5 to 10 seconds. This procedure increases the yield of cells and eliminates most of the cellular debris which adheres to the membrane of these cells. The cells were washed two additional times and resuspended to a concentration of 10^7 cells per ml in Hanks balanced salt solution.

Hepatocytes were isolated from liver by a procedure modified from Berry and

Friend.[2] Rats were anesthetized with ether, 100 units heparin injected intravenously into the dorsal vein of the penis, and the portal vein and thoracic portion of the inferior vena cava cannulated with blunt 21- and 16-gauge needles. The liver was removed, placed in a Petri dish and flushed with 30 ml of calcium-free Hanks solution before beginning the perfusion with enzyme solution. The liver, positioned about 10 cm above the reservoir, was perfused at a rate of 30 to 60 ml per minute by the use of a ministalic pump. The perfusion was continuously monitored to avoid distention of the liver. The enzyme medium was continuously gassed with a mixture of 95 percent O_2 and 5 percent CO_2. After 10 to 20 minutes the perfusate began to ooze freely from the surface of the liver, and the fluid was collected and returned to the reservoir. When the flow rate dropped to about 10 ml per minute, the perfusion was stopped, the liver trimmed of debris, chopped into fine pieces with scissors and transferred to siliconized 250-ml Erlenmeyer flask. Fresh enzyme solution (10 ml) was added and the suspension gently shaken by hand in a water bath at 37°. The suspension was then filtered through 60 micron nylon net and the cells separated by centrifugation at 50xG for 80 seconds. The supernatant was decanted and added back to the undigested liver fragments and the incubation procedure repeated. The cells obtained from the two incubations were combined, washed twice with calcium and glucose-free Hanks and resuspended to a concentration of 2×10^6 per ml.

The viability of Kupffer and hepatocyte suspensions was determined by trypan blue exclusion.[19] The viability of Kupffer cells was routinely greater than 95 percent; parenchymal cell viabilities ranged between 75 and 90 percent. Total cell counts were performed with crystal violet for Kupffer cells and trypan blue for parenchymal cells. The Kupffer cell suspension did not contain parenchymal cells, but did have 10 to 15 percent contamination with "lymphocytelike" and other unidentified cells. Parenchymal cells did not have any red cell contamination and contained less than one percent Kupffer cells.

Incubation Procedure

Cells were added to siliconized 25-ml Erlenmeyer flasks or 16 x 150 mm culture tubes and incubated with the labeled precursor,[14] C-amino acid, 0.5 μc or 5 μc ^{3}H-uridine for 30, 60, and 90 minutes with air as the gas phase. The final volume was 2.0 ml. The labeled precursor and the appropriate inhibitors were mixed with Hanks balanced salt solution, pH 7.4, immediately before use.

Analytical Procedures

After incubation at 37° an equal volume of ice-cold 10-percent TCA was added to stop the reaction. The pellets were washed twice with 5-percent trichloracetic acid (TCA) and nucleic acids isolated by the hot TCA extraction procedure of Schneider.[20] The TCA-precipitated protein was dissolved in 1 percent Na_2CO_3 — 1 N NaOH. An aliquout of the hot TCA supernatant or dissolved protein was transferred to a scintillation vial, 10 ml Aquasol added, and the samples counted in a liquid scintillation counter (Nuclear of Chicago). Efficiency of counting was determined by internal standardization using ^{14}C-toluene.

Protein content of cell precipitates was determined by the Lowry procedure.[21] RNA and DNA were measured by the orcinol and diphenylamine reactions respectively.[22]

RESULTS

A. Characteristics of Isolated Cells

Since approximately 5 to 6 hours are required to prepare suspensions of Kupffer cells, it was essential to determine the functional and metabolic competence of the liver macrophages. The Kupffer cell suspensions readily phagocytized ^{131}I-gel lipid emulsion, ^{32}P-labeled heat-killed and viable *Eschericia coli* or *Staphylococcus albus* 502A, sheep erythrocytes and 0.8 μ latex beads. Phagocytosis

of inert or viable particulates is dependent on the presence of serum and heparin as previously described.[6,7] Kupffer cells also killed 50 percent of a bacterial innoculum after two hours of incubation at 37° (Lentz, P. E., unpublished results).

Metabolism of isolated Kupffer cells has been investigated by Pisano et al.[6,23] and by Lentz and Di Luzio.[7] These studies demonstrated that the Kupffer cell suspensions did not respond to phagocytosis as do polymorphonuclear leukocytes[24] and alveolar macrophages[24] with increased oxidation of ^{14}C-1-glucose, formation of lactic acid, or oxygen consumption. In addition, metabolic inhibitors such as cyanide, iodoacetate or sodium flouride did not have significant effects on uptake of colloidal gold or gel lipid emulsion. Our studies[7] have confirmed that Kupffer cells do not exhibit an increased O_2 consumption during phagocytosis, but that they do increase the amount of glucose oxidized via the hexosemonophosphate shunt during phagocytosis (Lentz, unpublished results).

Recent studies have explored the ability of the Kupffer cell to actively transport alpha-aminoisobutyric acid across the cell membrane. An intracellular-to-extracellular ratio of 10 was found after two hours of incubation, indicating that these cells actively concentrate this model amino acid. The apparent active transport was reduced by a 10-degree reduction in temperature, but was unaffected by 2,4-dinitrophenol (0.1 mM) or a nitrogen atmosphere (Lentz, unpublished results).

These cells also exhibited the ability to "process" antigens and initiate an immune response when macrophages containing antigen or RNA extracted from macrophages after phagocytosis of antigen was injected into normal rats.[25]

These various parameters of phagocytic and metabolic activity suggest that active macrophages can be obtained from the liver by enzymatic means and that these cellular suspensions are suitable for investigation of the physiology of these cells. However, the relationship of the activities observed with these isolated cell suspensions *in vitro* to their behavior *in vivo* can not now be estimated. Crisp and Pogson[26] recently have evaluated several procedures for preparation of hepatic parenchymal cells and concluded that the enzymatic digestion procedure of Berry and Friend[2] produced good yields of cells with high retention of cytoplasmic enzymes and preservation of complex metabolic activities such as gluconeogenesis and albumin synthesis. At this time the cell suspensions obtained with the techniques of Berry and Friend appear to be superior for analyzing the biochemical and metabolic activities of hepatocytes.

B. Incorporation of ^{14}C-luecine in Total Liver Protein, Parenchymal Cells and Kupffer Cells *in vivo*

Leucine was selected as the tracer amino acid because it is not catabolized into other low molecular weight compounds to any significant extent, probably owing to a lack of transaminase, and is apparently used primarily for protein synthesis.[12] ^{14}C-leucine (6.5 μc) was injected intravenously and total liver homogenates, parenchymal cells or Kupffer cells prepared at 15, 30, 60 and 120 minutes after injection of the isotope. Total liver protein was rapidly and maximally labeled at 15 and 30 minutes and fell to about one half the peak specific activity at 60 and 120 minutes (Table 1). Parenchymal cell incorporation closely followed the pattern of whole liver. Liver macrophage protein had a low specific activity at 15 and 30 minutes, peaked at 60 minutes and rapidly declined at 120 minutes to a value similar to that observed in whole liver and parenchymal cells.

C. Effect of Actinomycin D on Protein Synthesis in Liver Kupffer and Parenchymal Cell Suspensions *in vitro*

Liver macrophages incorporated ^{14}C-leucine into trichloroacetic acid-precipitable proteins in a linear manner for more than two hours indicating that the necessary co-factors such as guanosine triphosphate, and the enzymatic ma-

TABLE I

INCORPORATION ^{14}C-LEUCINE BY TOTAL LIVER AND LIVER KUPFFER CELLS *IN VIVO*

Cell Suspension	Specific Radioactivity cpm/mg Protein			
	15 min	30 min	60 min	90 min
Liver Homogenate	711	741	284	318
Kupffer Cell	236	224	761	383

^{14}C-leucine injected intravenously and liver homogenates or Kupffer cells prepared after various periods of incorporation *in vivo*. The specific radioactivity of parenchymal cell corresponds to the whole liver homogenate. Data presented as mean value of three animals. Variation between animals was less than five percent.

chinery for protein synthesis remained intact after the lengthy isolation period. Actinomycin D inhibited the incorporation of the labeled amino acid according to the concentration of the drug in the incubation media (Table II). After 90 minutes of incubation in the prescence of 2.5, 12.5, 50 and 100 ug Actinomycin D per ml the percentage inhibition was 22, 35, 53 and 45 percent respectively. The inhibition of incorporation was observed after 30 minutes of incubation with concentrations of actinomycin D greater than 12.5 μg per ml. Low doses of actinomycin D (2.5 μg per ml) did not depress incorporation until 90 minutes after contact with the antibiotic, indicating that the antibiotic does not readily penetrate cellular membranes and reach an intracellular concentration sufficient to interfere with synthesis of messenger RNA or to disrupt ribosomes.

Protein synthesis by parenchymal cell suspensions *in vitro* was less sensitive to actinomycin D than was that by liver macrophages. Examination of the data in Table 1 shows that 50 and 100 μg actinomycin D per ml inhibited the incorporation of labeled amino acid by 9 and 23 percent in parenchymal cells after 90 minutes of incubation, whereas similar doses caused a 53 and 45 percent depression in liver macrophages.

TABLE II

EFFECT OF ACTINOMYCIN D (AD) ON THE INCORPORATION OF ^{14}C-LEUCINE INTO THE PROTEINS OF LIVER KUPFFER AND PARENCHYMAL CELL SUSPENSIONS *IN VITRO*

Cell Suspension	AD μg/ml	Specific Radioactivity cpm/mg X 10^{-3}		
		30 min	60 min	90 min
Kupffer	0	39	58	78
	2.5	37 (95)	58 (100)	57 (73)
	12.5	31 (84)	37 (65)	48 (65)
	50	28 (74)	34 (61)	34 (47)
	100	20 (51)	29 (55)	34 (55)
Parenchymal	0	2.2	3.0	3.4
	50	1.9 (88)	2.6 (84)	3.1 (91)
	100	1.7 (80)	2.2 (73)	2.7 (77)

Data presented as mean of three experiments with triplicate samples at each time interval. The values in parentheses give the percentage incorporation of the control cell suspension.

D. Effect of Actinomycin D on RNA Synthesis in Liver Kupffer and Parenchymal Cell Suspensions *in vitro*

Uridine labeled in the 5 position was used as an indicator of RNA synthesis because this nucleoside is a specific precursor of RNA. It will not label DNA because in the transformation of uridine to thymidine the 5-H label is lost.[27] All doses of actinomycin D inhibited the incorporation of uridine by liver macrophages (Table III). The percentage inhibition associated with 0.5, 2.5, 5.0 and 50 μg actinomycin D per ml was 33, 52, 62 and 73 percent after 90 minutes of incubation. All doses were inhibitory after 30 minutes of incubation, suggesting that actinomycin D readily penetrates the cell membrane and interferes with nuclear synthesis of RNA. This hypothesis was recently confirmed by the measurement of the intracellular concentration of ^{3}H-actinomycin D. The antibiotic reached its maximum concentration within 10 minutes of incubation (Lentz, unpublished results).

Similar experiments with the parenchymal cell suspensions have produced a *stimulation* of incorporation after 30 minutes and a *depression* after 90 minutes of incubation.

E. Effect of Chloramphenicol (CAP) on Protein and RNA Synthesis in Liver Macrophages and Parenchymal Cells *in vitro*

Chloramphenicol, a classical inhibitor of bacterial protein synthesis, had no effect on the incorporation of ^{14}C-leucine into proteins of liver macrophages but did inhibit incorporation of the labeled amino acid by parenchymal cells (Table IV). Incorporation of uridine was stimulated in both cell suspensions by all concentrations of chloramphenicol after 30 minutes of incubation (Table V). After 60 or 90 minutes there was a depression of RNA synthesis by Kupffer cells. Parenchymal cell RNA synthesis was slightly depressed after 60 minutes and was normal or slightly stimulated after 90 minutes of contact with chloramphenicol.

F. Effect of Puromycin on Incorporation of ^{14}C-leucine by Liver Macrophages *in vitro*

Puromycin (1×10^{-4}M) completely inhibited the incorporation of labeled amino acids by liver macrophages *in vitro* (Table VI). Casanello and Gerchenson[17] have recently demonstrated complete suppression of protein synthesis *in vitro*

TABLE III

EFFECT OF ACTINOMYCIN D ON THE INCORPORATION OF ^{3}H-URIDINE INTO THE RNA OF LIVER KUPFFER AND PARENCHYMAL CELL SUSPENSIONS *IN VITRO*

Cell Suspension	AD μg/ml	Specific Radioactivity cpm/mg X 10^{-3}		
		30 min	60 min	90 min
Kupffer	0	47	88	111
	0.5	35 (76)	55 (62)	84 (67)
	2.5	29 (55)	50 (47)	68 (48)
	5.0	23 (48)	30 (30)	55 (38)
	50.0	8 (17)	15 (14)	27 (19)
Parenchymal	0	172	146	286
	5.0	285 (165)	145 (98)	198 (69)
	50.0	19 (10)	27 (18)	23 (8)

Data are presented as mean values from three replicate tubes. The values in parentheses give the percentage incorporation of control cell suspensions after the specified incubation period.

TABLE IV

EFFECT OF CHLORAMPHENICOL (CAP) ON THE INCORPORATION OF ^{14}C-LEUCINE INTO PROTEINS OF LIVER KUPFFER AND PARENCHYMAL CELLS *IN VITRO*

Cell Suspension	CAP μg/ml	Percent Control		
		30 min	60 min	90 min
Kupffer	.08	98	106	100
	8	103	94	96
	40	99	96	100
	80	102	99	84
Parenchymal	.08	75	70	56
	8	50	50	26
	40	33	25	12
	80	16	35	6

Data presented as mean percentage of incorporation of cell suspensions not incubated with chloramphenicol.

TABLE V

EFFECT OF CHLORAMPHENICOL (CAP) ON THE INCORPORATION OF ^{3}H-URIDINE INTO RNA OF LIVER KUPFFER AND PARENCHYMAL CELLS *IN VITRO*

Cell Suspension	CAP μg/ml	Percent Control		
		30 min	60 min	90 min
Kupffer	.08	142	76	74
	8	160	76	74
	40	59	50	71
	80	129	—	64
Parenchymal	.08	140	75	130
	8	108	63	112
	40	120	87	142
	80	168	104	106

Data presented as percentage incorporation of cells not incubated with chloramphenicol.

TABLE VI

EFFECT OF PUROMYCIN ON THE INCORPORATION OF ^{14}C-LABELED AMINO ACIDS INTO THE PROTEINS OF KUPFFER CELL SUSPENSIONS *IN VITRO*

Experiment Number	Precursor	Puromycin 1×10^{-5}M	Specific Radioactivity of Protein cpm/mg		
			30 min	60 min	90 min
1	^{14}C-leucine	—	29,891	54,814	71,814
		+	669 (98)	729 (99)	865 (99)
2	^{14}C-labeled	—	22,872	37,301	47,456
	Amino Acid	+	2,013 (91)	2,117 (95)	2,481 (94)
	Mixture				

The concentration of ^{14}C-leucine or ^{14}C-amino acid mixture was 0.5 uc per 2 ml. The number in parentheses is the percentage inhibition of the incorporation.

in liver parenchymal cells. However, we have not attempted to confirm their observation with hepatocytes prepared by the procedure of Berry and Friend.[2]

DISCUSSION

There is growing interest in the metabolic and biochemical characteristics of discrete cell populations of mammalian liver. Analysis of specific cell types *in vitro* has the distinct advantage of immediate contact with drugs and labeled precursors and freedom from the influences of other cell types, blood-borne hormones and circulating metabolites. However, dispersion of a tissue by enzymatic, mechanical or chelation techniques may produce cell suspensions which have little morphological, functional or biochemical resemblance to the cell *in situ*. In recent years several techniques for preparation of liver macrophages and hepatocytes have been published. These techniques produce good yields of cells which retain soluble enzymes[2,26] complex metabolic activities of protein synthesis,[4,13,15-17] nucleic acid synthesis,[13,14,16] gluconeogenesis,[2] ethanol oxidation,[27] albumin synthesis,[29,30] and drug metabolism.[31-33] The volume of literature on the properties of isolated hepatocytes clearly indicates that several criteria of cell viability are required to adequately assess the metabolic competence of cell suspensions prepared from liver. These data can however provide only partial answers to the question of whether all of the functions of a specific cell population are retained in any given preparation.

This report describes the incorporation of labeled precursors by rat liver macrophages and the sensitivity of two populations of rat liver cells to commonly used inhibitors of protein and nucleic acid synthesis. Leucine was readily incorporated by both parenchymal and Kupffer cells *in vivo*. The data suggest that proteins are rapidly and extensively labeled in the hepatocyte or whole liver and then probably secreted. Morgan and Peters[10] have shown that approximately 20 minutes are required for newly synthesized albumin to reach the blood. Since serum proteins are the major proteins synthesized by adult rodent liver,[33] the decline in specific activity of total liver homogenate and parenchymal cell protein probably reflects this secretory activity. We have not incubated the parenchymal cells for varying periods *in vitro* after isolation and examined the media for labeled albumin. Weigand *et al.*[29] have demonstrated synthesis and secretion *in vitro* of albumin by hepatocytes prepared by a procedure similar to that used here.

Destruction of parenchymal cells and release of nascent protein during the isolation procedure is a possible explanation for the decline in specific activity of total proteins at one and two hours after injection of the isotope. There is unfortunately no method available which yields absolute recovery of hepatocytes, and a certain but minimal percentage of cells are disrupted during dispersion of the liver. An alternate explanation for these data is the selective isolation of parenchymal cells which had not been adequately exposed to the labeled amino acid or which were not active in protein synthesis. There are apparent zonations of metabolic activity within the liver lobule as reflected by histochemical techniques,[35] but there are no reported zones of protein synthesis. At this time it is our contention that representative populations of hepatocytes are obtained with the technique of Berry and Friend[2] and that there is no reliable technique for estimating the percentage of cells obtained from various locations within the lobule.

The significance of the delayed peak as well as the decline in specific activity in the liver macrophage is unclear because proteins are not thought to be rapidly secreted from or turned over by these cells. Strecher[36] has demonstrated that some components of complement, particularly C1 and C4 were synthesized in liver macrophages. Ashley and Peters[12] have demonstrated by autoradiography a consistent and persistent level of protein synthesis estimated to represent about 5 percent of the total liver

protein within liver reticuloendothelial cells. It is unlikely that selective isolation or destruction of Kupffer cells has occurred during the preparation of the cell suspensions. An examination of the media for proteins may reveal the presence of secretory activity by these cells.

The data obtained suggest that the liver parenchymal cells readily synthesized and secreted proteins, whereas the Kupffer cells had a slower rate of synthesis and perhaps secretion of proteins.

There are two possible interpretations for the effect of actinomycin D on the incorporation of ^{14}C-leucine by liver macrophages *in vitro*. First, continued synthesis of messenger RNA may be required to maintain protein synthesis by liver macrophages during the *in vitro* incubation. There are no reports on the stability of messenger RNA in liver macrophages, and until such data are available this hypothesis must be questioned. A second interpretation involves the disruption of polyribosomes and free ribosomes or the enzymatic machinery for protein synthesis by actinomycin D.[37] We have not yet examined the sedimentation profiles of ribosomes isolated from these cells, and it would be interesting to determine the status of these key elements for protein synthesis after incubation with actinomycin D. The insensitivity to actinomycin D of amino acid incorporation by parenchymal cells indicates that much of the protein synthesized by parenchymal cells *in vitro* used messenger RNA present in the cells before the incubation began. The resistance of protein synthesis in parenchymal cells confirms the data of Shanmugan and Bhargava with hepatocytes prepared by mechanical means.[13] Our data would also agree with Revel and Hiatt[37] on the stability of "liver" messenger RNA. If future studies indicate that the doses of actinomycin D used here did not destroy ribosomes in liver macrophages, a striking difference between the physiology of the liver macrophage and the hepatocyte will be evident.

Actinomycin D is a classical inhibitor of DNA-directed RNA synthesis. All doses of actinomycin D used in this study were sufficient to depress but not completely inhibit nuclear and cytoplasmic RNA synthesis in liver macrophages and hepatocytes. These results differ markedly from those of Shanmugan and Bhargava, who demonstrated a definite inhibition of RNA synthesis by actinomycin D after 180 and 240 minutes of *in vitro* incubation.[13] Other investigators[13] with a variety of cells in culture have demonstrated that 1 μg of antibiotic per ml or less inhibited RNA synthesis by 90 percent. Perhaps the remarkable sensitivity of cells maintained in culture reflects another aspect of the dedifferentiated cell. It is difficult adequately to explain the stimulation of RNA synthesis after 30 minutes and the depression after 90 minutes. This paradoxical behavior may be a reflection of altered membrane permeability, transport of the antibiotic, or the time required for the antibiotic to accumulate within the nucleus. A detailed analysis of nuclear and cytoplasmic RNA synthesis in parenchymal cells after exposure to various doses of actinomycin D is required to explain adequately the effects observed in this study.

Inhibition of protein synthesis in liver parenchymal cells by chloramphenicol has not been previously reported. Intact reticulocytes and tumor cells were not inhibited by chloramphenicol.[38,39] Nirenberg and Matthei[40] were able to demonstrate almost complete inhibition of protein synthesis in an *E. coli* cell free system with 0.15 μmoles of this drug. The mechanism of protein synthesis inhibition by chloramphenicol is thought to involve blocking the attachment of messenger RNA to the ribosome.[41] A more novel mechanism proposed by Talal and Exum[42] implicates a binding of chloramphenicol only to ribosomes attached to endoplasmic reticulum and not to those free in the cytoplasm. This mechanism if correct can adequately explain our failure to observe inhibition of protein synthesis by Kupffer cells exposed to chloramphenicol. In mature rats these cells contain more free ribosomes than bound ribosomes,[43] and perhaps this

accounts for their resistance to chloramphenicol. However, other interpretations, such as failure of the drug to cross membranes of the Kupffer cells, should be considered before selecting the mechanism of Talal and Exum. The same mechanism can explain our results with the parenchymal cell suspensions; however, a change in permeability of the parenchymal cell membrane after dispersion of the tissue would have to be excluded first. Synthesis of mitochondrial proteins has been shown by Gonzales-Cadavid to be sensitive to chloramphenicol.[44] Whether the depression in protein synthesis observed in suspensions of hepatocytes exposed to chloramphenicol is a reflection of a suppression in mitochondrial protein systhesis was not evaluated.

Our data on RNA synthesis which indicate a slight stimulation during exposure to chloramphenicol agree with those of Le Page[39] with ascites tumor cells and Breitman and Webster[45] with calf thymus nuclei suspensions. Jacob and Bhargava[46] demonstrated complete inhibition of RNA synthesis in parenchymal cells when adenine or uracil was used as the precursor, indicating that the drug interferes with the enzymatic conversion of the base into the nucleoside monophosphate.

Acknowledgement

The technical assistance of Mrs. John Hobart is greatly appreciated.

References

1. Daoust R: The cell population of liver tissue and the cytological reference bases. In Liver Function. Ed. by R. W. Brauer. Am Inst Biol Sci 1965, p. 3-10

2. Berry MN, Friend DS: High-yield preparation of isolated rat liver parenchymal cells. J Cell Biol **43**:506-520, 1969

3. Howard R, Christenson A, Gibbs F, Pesch L: The enzymatic preparation of isolated intact parenchymal cells from rat liver. J Cell Biol **35**:675-684, 1967

4. Jacob S, Bhargava P: A new method for preparation of liver cell suspensions. Exp Cell Res **27**:453-468, 1962

5. Gallai-Hatchard JL, Gray, GM: A method of obtaining a suspension of intact parenchymal cells from adult rat liver. J Cell Sci **8**:73-86, 1971

6. Pisano JC, Filkins JP, Di Luzio NR: Phagocytic and metabolic activities of isolated rat liver cells. Proc Soc Exp Biol Med **128**:917-922, 1968

7. Lentz PE, Di Luzio NR: Biochemical characterization of Kupffer and parenchymal cells isolated from rat liver. Exp Cell Res **67**:17-26, 1971

7a. Lentz PE, Di Luzio NR: Phagocytic, bactericidal and metabolic activities of rat alveolar macrophages exposed *in vitro* to aqueous extracts of tobacco smoke. Unpublished data

8. Henshaw EC, Hirsch CA, Morton BE, Hiatt HH: Control of protein synthesis in mammalian tissues through changes in ribosome activity. J Biol Chem **246**:436-446, 1971

9. Schimke RT, Ganschow R, Doyle D, Arias IM: Regulation of protein turnover in mammalian tissues. Fed Proc **27**:1223-1230, 1968

10. Morgan EH, Peters T: Intracellular aspects of transferrin synthesis and secretion in the rat. J Biol Chem **246**:3508-3511, 1971

11. Ficq A: Radioautographic studies on nuclear activity in the liver. J Histochem Cytochem **7**:215-223, 1959

12. Ashley CA, Peters T: Electron microscopic radioautographic detection of sites of protection synthesis and migration in liver. J Cell Biol **43**: 237-249, 1969

13. Shanmugam G, Bhargava PM: The effect of actinomycin D on the synthesis of ribonucleic acid and protein in rat liver parenchymal cells in suspension and liver slices. Biochem J **108**:741-748, 1968

14. Jacob S, Bhargava PM: Synthesis of ribonucleic acid by liver cells in suspension. Biochem J **95**:568-576, 1965

15. Burton DN, Collins JM, Porter JW: Biosynthesis of the fatty acid synthetase by isolated rat liver cells. J Biol Chem **244**:1076-1083, 1969

16. Jezyk PF, Liberti JP: Metabolic activities of mechanically and enzymatically prepared rat liver cells. Arch Biochem Biophys **134**:442-449, 1969

17. Casanello DW, Gerschenson LE: Some morphological and biochemical characteristics of isolated rat liver cells dissociated with sodium tetraphenylboron and cultured in suspension. Exp Cell Res **59**:283-290, 1970

18. Steinberg MS: "ECM" its nature, origin and function in cell aggregation. Exp Cell Res **30**:257-279, 1963

19. Hanks JH, Wallace RE: Determination of cell viability. Proc Soc Exp Biol Med **71**:188-192, 1958

20. Schenider WC: Phosphorous compounds in animal tissues. Extraction and estimation of desoxypentose nucleic acid and of pentose nucleic acid. J Biol Chem **161**:293-303, 1951

21. Lowry OH, Rosebrough NJ, Farr AL, Randall RJ: Protein measurement with the folin phenol reagent. J Biol Chem **193**:265-275, 1951

22. Fleck A, Munro H: The determination of nucleic acids. *In* Methods of Biochemical Analysis. Ed. by D. Glick, New York, Interscience Publishers **14**:113-176, 1966

23. Pisano JC, Filkins JP, Di Luzio NR: Metabolic characterization of actively phagocytizing isolated rat Kupffer cells. J Reticuloendothel Soc **8**:25-36, 1971

24. Oren R, Farnham A, Saito K, Milofsky E, Karnovsky M: Metabolic patterns in three types of phagocytizing cells. J Cell Biol **17**:487-501, 1963

25. Lentz PE, Di Luzio NR: Comparative evaluation of immunogenic RNA of liver, spleen and peritoneal macrophages. Unpublished data

26. Crisp DM, Pogson CI: Glycolytic and gluconeogenic enzyme activities in parenchymal and non-parenchymal cells from mouse liver. Biochem J **126**:1009-1023, 1972

27. Haynoe FG, Quaglino D: Autoradiographic investigations of RNA and DNA metabolism of human leucocytes cultured with phytohemagglutin; ^{3}H-uridine as a specific precursor of RNA. Nature **205**:151-154, 1965

28. Berry MN: The action of pyruvate on ethanol oxidation by intact isolated liver cells. Biochem J **123**:400, 1971

29. Weigand K, Muller M, Urban J, Schreiber G: Intact endoplasmic reticulum and albumin synthesis in rat liver cell suspensions. Exp Cell Res **67**:27-32, 1971

30. Leffert HL, Paul D: Studies on primary cultures of differentiated fetal liver cells. J Cell Biol **52**:559-568, 1972

31. Henderson P, Dewaide JH: Metabolism of drugs in isolated rat hepatocytes. Biochem Pharmacol **18**:2087-2094, 1969

32. Henderson P: Phenobarbital induction of UDPP-glucuronyl transferase in isolated rat hepatocytes. Life Sci **10**:655-660, 1971

33. Cantrell E, Bresnick E: Benzpyrene hydroxylase activity in isolated parenchymal and non-parenchymal cells of rat liver. J Cell Biol **52**:316-321, 1972

34. Ryoo H, Tarver H: Studies on plasma protein synthesis with a new liver perfusion apparatus. Proc Soc Exp Biol Med **128**:760-772, 1968

35. Wachstein M: Cyto- and histo-chemistry of the liver. In *The Liver*. Ed. by CH Rouiller. New York, Academic Press, **1**:137-194, 1963

36. Strecher V: Synthesis of proteins by mononuclear phagocytes. *In* Mononuclear phagocytes. Ed. by R van Furth. Philadelphia, FA Davis Company, 1970, p. 133-150

37. Revel M, Hiatt HH: The stability of liver messenger RNA. Proc Nat Acad Sci **51**:810-818, 1964

38. Borsook H, Fischer EH, Keighley G: Factors affecting protein synthesis in vitro in rabbit reticulocytes. J Biol Chem **229**:1059-1070, 1957

39. Le Page GA: Effects of chloramphenicol or incorporation of glycine-2-^{14}C into mammalian tumor cell proteins and purines. Proc Soc Exp Biol Med **83**:724-726, 1953

40. Nirenberg MW, and Matthei JH: The dependence of cell-free protein synthesis upon naturally occurring or synthetic polyribonucleotides. Proc Nat Acad Sci **47**:1588-1602, 1961

41. Weisberger AS: Inhibition of protein synthesis by chloramphenicol. Ann Rev Med **18**:483-494, 1967

42. Talal N, Exum ED: Two classes of spleen ribosomes with different sensitivities to chloramphenicol. Proc Nat Acad Sci **55**:1288-1295, 1966

43. Rouiller C, Jezequel A: Electron microscopy of the liver. *In* The Liver. Ed. by CH Rouiller. New York, Academic Press, 1963, **1**:195-264

44. Gonzalez-Cadavid NF, Bello EMA, Ramirez JL: Differential long term effects of D-chloramphenicol on the biogenesis of mitochondria in normal and regenerating rat liver. Biochem J **118**: 577-586, 1970

45. Breitman TR, Webster GC: Effect of chloramphenicol on protein and nucleic acid synthesis in isolated thymus nuclei. Biochem Biophys Acta **27**:408-409, 1958

46. Jacob ST, Bhargava PM: Effect of chloramphenicol on ribonucleic acid synthesis in liver cells in suspension. Biochem J **97**:67-73, 1965

A NOVEL BILE PIGMENT-PORPHYRIN COMPLEX INDUCED BY ALLYLISOPROPYLACETAMIDE AND PREVENTED BY INGESTION OF LEAD*

George Y. Hsu

Abstract. *Rats fed allylisopropylacetamide (AIA) (Sedormid®), a barbiturate, developed a mild hepatic porphyria. This was accompanied by appearance of an abnormal, viscous, highly insoluble, dark brown pigment in intrahepatic biliary ducts. This novel pigment dissolved in dilute formic acid, and a pink ultraviolet fluorescent substance with the spectrum of a porphyrin appeared in the extract. Ultraviolet microscopy disclosed that this substance was derived from the abnormal intraductal pigment. When the animals were fed lead subacetate, which induced a severe erythropoietic porphyria, numerous renal cortical neoplasms developed but the abnormal bile pigment characteristic of the induced hepatic porphyria did not appear. When rats were fed both the barbiturate and lead subacetate, the pigment rarely appeared in the bile ducts, and development of renal tumors was inhibited. It seemed that prevention by lead of formation of the bile pigment-porphyrin complex was due to a block of aminolevulinic acid (ALA) dehydratase action by lead. Hence, the delta ALA normally converted to porphobilinogen by ALA dehydratase could not enter the porphyrin synthetic pathway. Thus, the excess ALA produced by barbiturate induction of ALA synthesase, though converted to porphyrin and complexed to bile pigment in animals fed the barbiturate, was prevented from such a conversion by lead and was excreted in the urine. The occurrence of the intrahepatic biliary tract disease was thereby prevented.*

The discovery of an abnormal bile pigment occurred during a study of combinations of hepatic and erythropoietic porphyria in the rat. Hepatic porphyria was produced by a diet containing a barbiturate, AIA (Sedormid®). Erythropoietic porphyria was produced by a dietary supplement of lead subacetate. Animals fed the barbiturate alone developed a mahogany-brown, highly insoluble bile pigment (Fig. 1). This filled many intrahepatic bile ducts and seemed not to be obstructive but passed sluggishly down the ducts. Animals fed lead subacetate with the barbiturate seldom developed the pigment.

MATERIALS AND METHODS

More than 700 Sprague-Dawley male and female rats, about four to six weeks old and weighing 50 to 125 gm, were used. They were divided into four groups. Group L consisted of 482 surviving rats fed the basal diet containing 1 percent lead subacetate. Group LS consisted of

From the Department of Pathology, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois

This work was supported by grants 2G-129 and NS-04872, United States Public Health Service and the Otho S. A. Sprague Memorial Institute

George Y. Hsu, M.D., Resident in Pathology, Presbyterian-St. Luke's Hospital; Assistant in Pathology, Rush Medical College

*Hektoen Award, First Prize, Chicago Pathologic Society, 1971

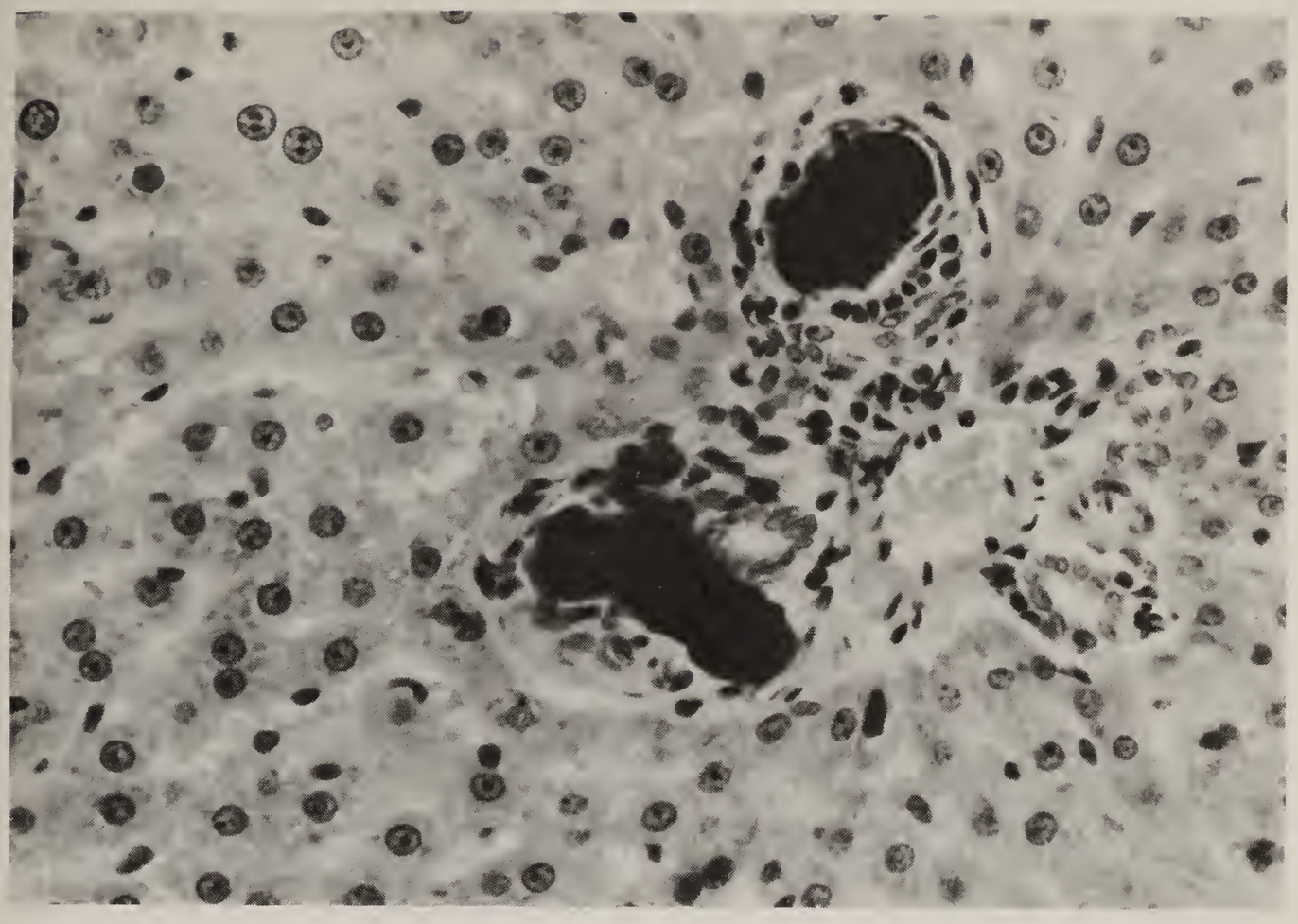


Fig. 1—Sprague-Dawley rats were fed 0.5 percent Sedormid diet for a period of 20 weeks. Note the accumulation of dark bile pigment filling the bile ducts. The portal triads are otherwise normal. No canalicular bile plugging is noted. H&E 450X

124 surviving rats fed the basal diet containing 1 percent subacetate and 0.5 percent allylisopropylacetamide (AIA). Group S consisted of 77 surviving rats fed the basal diet containing 0.5 percent AIA. Group N consisted of 24 rats fed the basal diet without supplements.

The animals were weighed each week and a record kept of the amount of diet consumed. Twenty-four hour specimens of urine were collected each month in individual ice-cold containers. These specimens were stored at −5° C prior to chemical analysis for coproporphyrin III[1], delta ALA[2], and lead by conventional atomic absorption spectrophotometry. Blood hemoglobin levels were obtained each month. At the end of experimental periods, varying from about 3 to 18 months, animals from each group were studied at autopsy. Blocks of tissue from all organs were fixed in 10 percent formalin, embedded in paraffin, and sections for microscopic study stained with hematoxylin and eosin. Other blocks of tissue, especially of the liver and kidney, were either stored at −20° C or studied, while fresh, immediately after death.

The studies of fresh liver, which concern us here, were done as follows: Thin frozen sections were made with a freezing microtome. A section was mounted on a glass slide and studied microscopically. If an abnormal brown pigment was easily recognized in the bile ducts, further studies were made. The remaining hundreds of thin frozen sections were divided into several lots and treated with various solvents as follows: distilled water, isotonic aqueous NaCl, isotonic phosphate buffer solutions (pH 2-11), neutral aqueous solutions of NaCl (1-10 percent), graded ethanol (70-100 percent), ethyl

ether, 0.01-0.1 N aqueous HCl, and 0.01-0.1 N aqueous NaOH. Finally, various concentrations of formic acid were used. Extracts of the sections of fresh liver were exposed to ultraviolet light, and the absorption spectrum measured.

The most suitable extraction of the abnormal intraductal biliary pigment occurred in 30 percent aqueous formic acid. These extracts fluoresced pink in ultraviolet light and had a maximal absorption at 400 mu[3] (Fig. 2). In order to assess the relation between this effect and changes induced in the sections of liver by the solvent, a special technique was devised. A thin section of fresh liver, cut with a freezing microtome, was mounted on a glass slide. One side of a thin glass coverslip was coated with a transparent gel made by dissolving 0.5-1.0 gm of gelatin in 100 ml of 30-percent aqueous formic acid. The side of the coverslip coated with the gelatin-formic acid semisolid medium was then pressed against the thin section of liver on the glass slide. The section was then studied with the ultraviolet microscope to determine the effect of the embedding medium on the various components of the liver. As these observations were being made, photographs of changes during exposure of the tissue to the formic acid-gelatin medium were taken. After a few minutes the section was examined with the light microscope, particular attention being given to changes which had occurred in the intraductal pigment during its exposure to the formic acid solution of gelatin.

RESULTS

Data on Urinary Excretion of Delta Aminolevulinic Acid, Coproporphyrin III and Lead

Animals fed the diet supplemented with lead subacetate alone had the slowest rate of growth. At the end of 40 weeks on this diet the average body weight was about 400 gm. The average

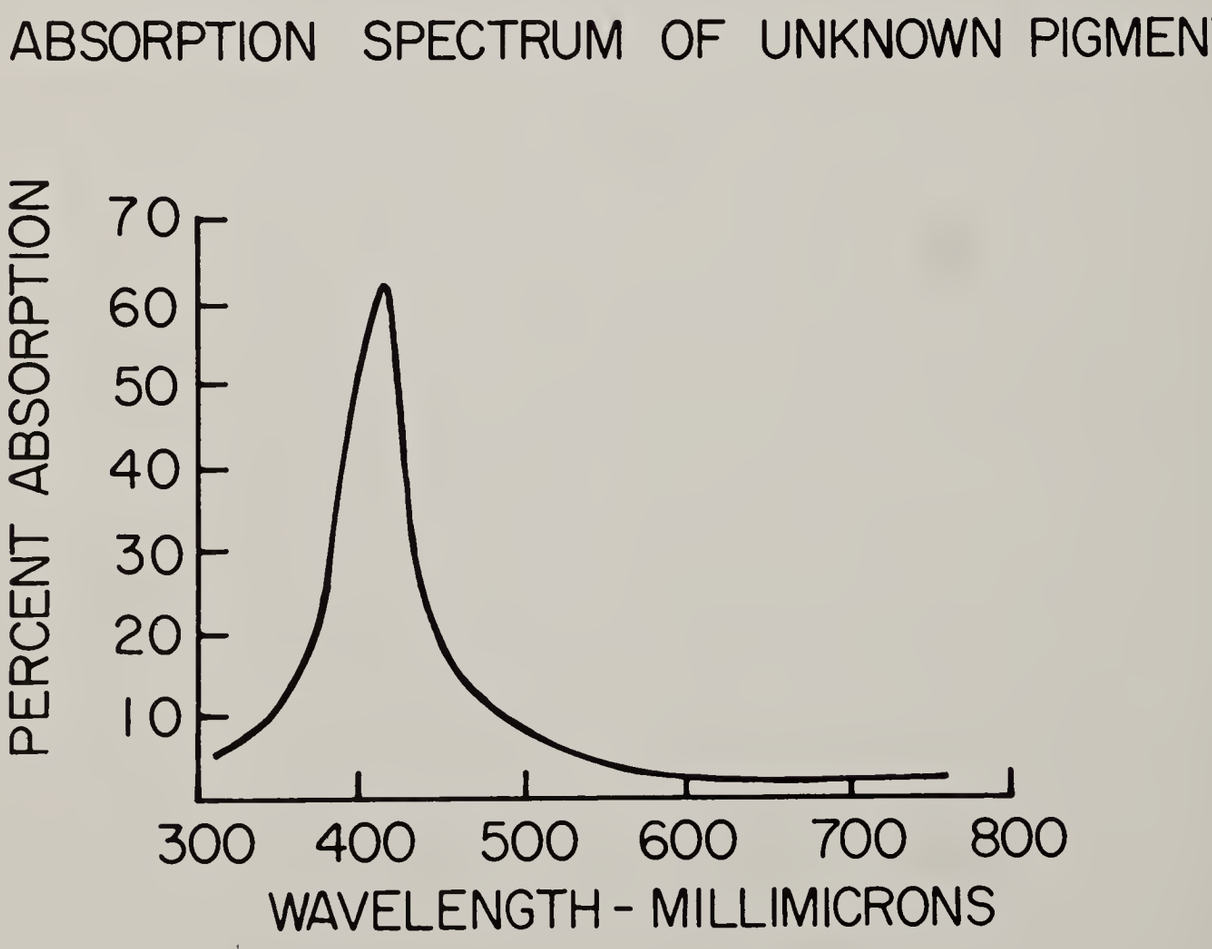


Fig. 2

blood hemoglobin level, which initially was 14 to 15 gm percent, gradually fell to 7 to 8 gm percent and remained there despite prolongation of the regimen. The average daily urinary excretion of ALA increased within about 30 days to approximately 1000 μg and continued to rise to 2000 to 2500 μg where it tended to remain throughout succeeding weeks or months (Fig. 3). During the same period normal control animals excreted an average of less than 100 μg of ALA each day. The average daily urinary excretion of lead was about 20 to 30 μg among the group fed lead subacetate, while a negligible or indeterminate amount was excreted by the control group. The average daily excretion of coproporphyrin III rose promptly to about 80 μg and remained near that level as long as the regimen was maintained (Fig. 4). Control animals excreted less than about 10 μg of coproporphyrin III each day in the urine.

The group (LS) fed lead subacetate and AIA gained weight more rapidly than the preceding group (L) having an average weight of about 450 gm at the end of 40 weeks of the regimen. Patterns of reduction in the level of blood hemoglobin and urinary excretion of lead resembled those of the groups fed lead subacetate alone. However, on the average, the LS group had a greater average daily excretion of coproporphyrin III and AIA in the urine than the L group (Figs. 3,4). This was about 3000 μg of ALA and 120 μg of coproporphyrin III per day.

The group (S), fed AIA alone, had a normal growth rate, rising at the end of 40 weeks to an average of about 550 gm. The blood hemoglobin level remained at a level of 14 to 15 gm percent. The pattern of excretion of ALA in the urine varied between about 100 to 150 μg

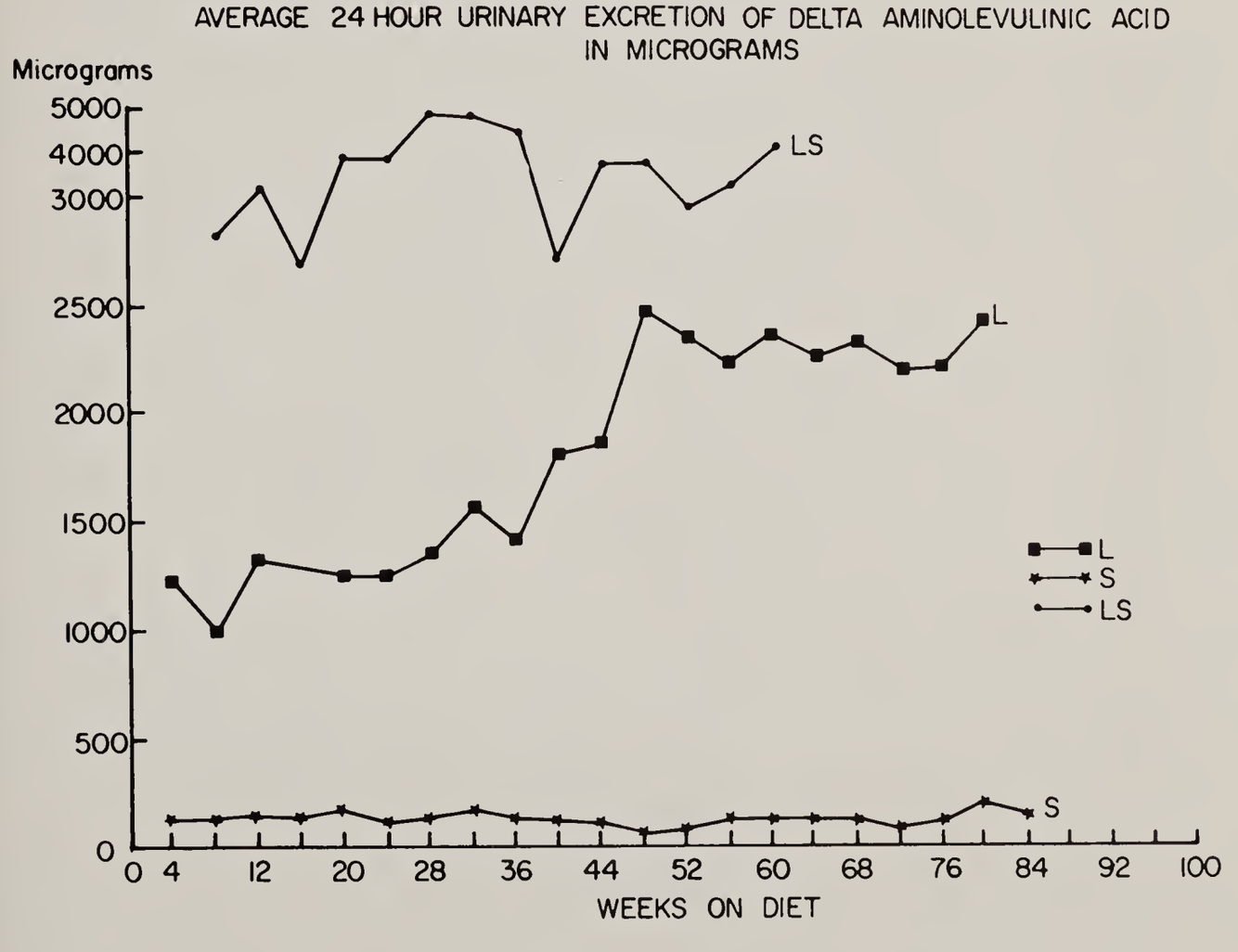


Fig. 3

each day (Fig. 3). The average daily excretion of coproporphyrin III was about 30 μg (Fig. 4). The excretion of lead in the urine was negligible or indeterminate.

Pathologic Findings

The group (L) fed lead subacetate during the first few weeks showed increasing erythropoietic activity in the spleen and bone marrow. This was accompanied by a variable accumulation of demonstrable iron, presumably hemosiderin, in the reticuloendothelial system and hepatocytes. After about six months on the regimen, epithelial tumors began to appear in the renal cortex. The first tumors to appear were cystomas. Later, these were accompanied by papillary cystomas and still later by adenomas. Invasive carcinomas with metastases did not appear until after 15 months. In no instance was there any evidence of hepatic disease, other than that accompanying accumulation of iron in the Kupffer cells and hepatocytes.

The group (S), fed the barbiturate (AIA), had no disease other than an accumulation of an atypical highly insoluble pigment in the biliary ducts (Fig. 1). This pigment was mahogany-brown in color. At times it seemed to have concentric laminations. Usually it completely filled the lumen of many of the small bile ducts. It could not be traced into the canaliculi though tiny granules of similar pigment were, at times, present in the cytoplasm of hepatocytes. There was no evidence of accumulation of the pigment in Kupffer cells but in some instances it had apparently been extruded from small bile ducts and engulfed by periductal macrophages (Fig. 1). The pigment began to appear in the ductal system after about 3 to 4 months. It tended to increase in amount

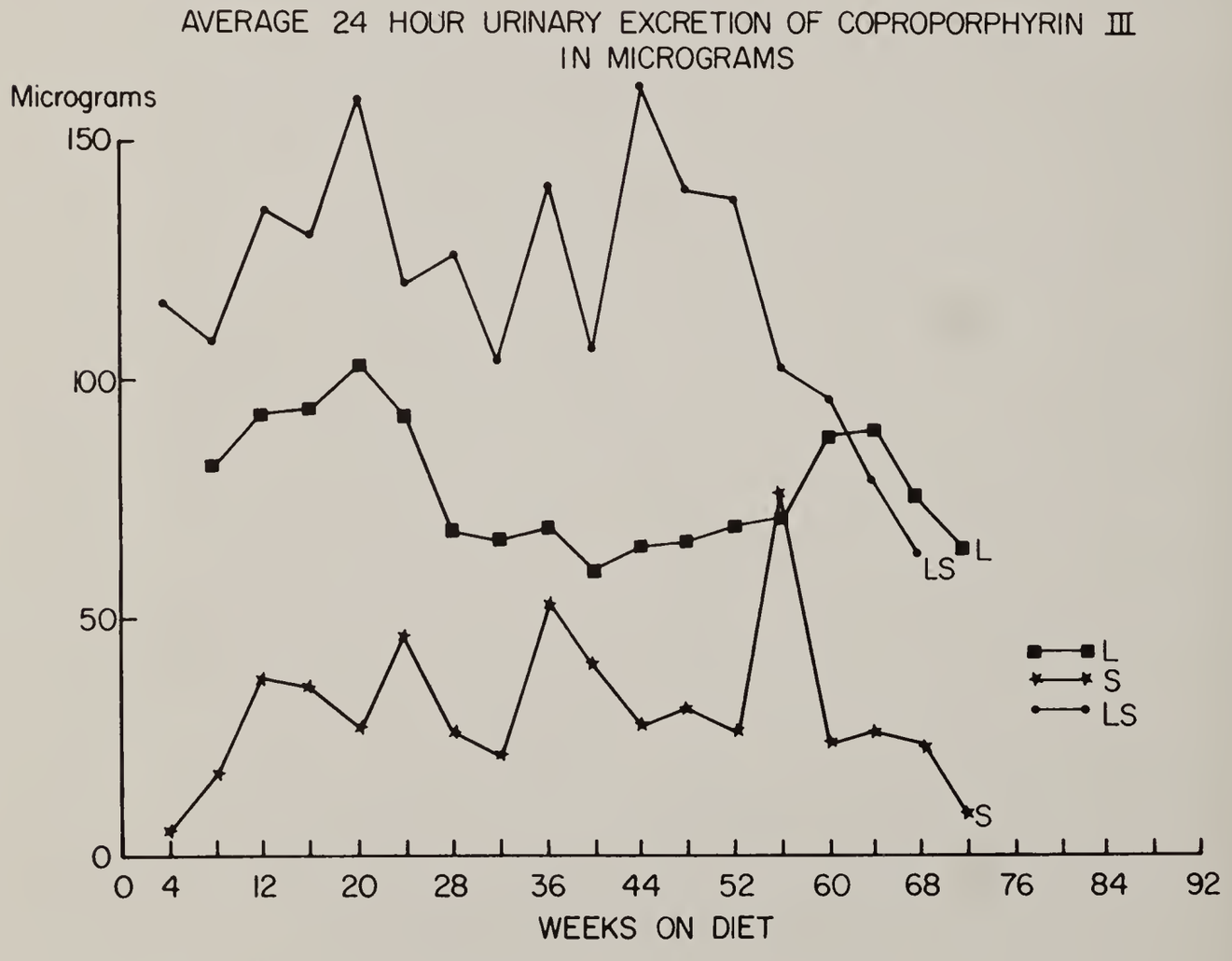


Fig. 4

until about 12 months, after which it decreased in amount. Among the 77 animals on this regimen only three had no pigment in the ductal system. Of these, two had been on the regimen more than 80 weeks. A puzzling feature was the lack of evidence of retrograde biliary tract obstruction due to the plugs of this abnormal pigment. For this reason, even though the pigment often resembled bile encountered in ducts as a result of prolonged stasis, we have assumed that the bile and associated pigment must have flowed in a reasonably normal way into the main large biliary ducts.

When a study was made of the animals fed lead subacetate, no abnormal intraductal biliary pigment was found.

When a study was made of the livers of animals fed lead subacetate along with the barbiturate (AIA), it was noted that there was a great reduction in the incidence and amount of the abnormal pigment. Among 124 rats, there were 14 animals with a small amount of pigment in a few small ducts. This occurred in 4 out of 68 animals of one series on the regimen for 25 to 68 weeks and in 10 of 56 animals of a series on the regimen for 46 to 86 weeks. While these observations were being made, it was noted that supplementation of the lead subacetate diet with the barbiturate greatly reduced the incidence of renal cortical epithelial tumors. No specific relation between the reduced incidence of tumors and the occasional occurrence of the abnormal biliary pigment in the group (LS) was apparent.

Chemical Study of the Abnormal Intraductal Bile Pigment

Thin frozen sections cut from blocks of fresh liver with a freezing microtome were used. These were suitable for immediate microscopic study. When the abnormal pigment was conspicuous in most of the biliary ducts, the sections were subjected to extraction and the results of the extraction with various reagents determined by re-examination of the section, microscopically. Among the large number of reagents used, the only reagent which extracted the abnormal biliary pigment without undue disruption of hepatic structure was dilute aqueous formic acid. At about 20 to 30 percent concentration of formic acid, an optimal relation between solution of the biliary pigment and retention of tissue structure was reached. Under this condition the dark mahogany-brown pigment filling the ducts first acquired a light yellow color and usually then dissolved. The reagent used for extraction remained colorless. When the extract was then exposed to ultraviolet light, it displayed a bright pink fluorescence. The appearance of this property in the extract paralleled the changes in the color and solubility of the abnormal intraductal biliary pigment. Similar changes in extracts of liver which had no pigment of this type were not encountered. The absorption spectrum of the extracts disclosed a peak at 400 mμ indicating the probable presence of a porphyrin compound (Fig. 2).

In order to assess the relation between the porphyrin compound appearing in the extract and the abnormal biliary pigment, ultraviolet microscopy was used. When the thin sections of liver, embedded in a semisolid gelatin medium, were viewed with an ultraviolet microscope, the intraductal plugs of abnormal biliary pigment remained dark. When the sections were embedded in a semisolid formic acid-gelatin medium, within a few seconds a bright pink band of fluorescence spread from the margins of the biliary pigment into the embedding medium. On changing the light source to a conventional lamp, it was noted that the abnormal biliary pigment had changed from mahogany-brown to a light yellow color, and in time disappeared from the ducts. These findings strongly supported the probability that we were dealing with a highly insoluble bile pigment-porphyrin complex which was dissociated by the formic acid with the release of porphyrin which appeared in the formic acid extract. We have yet to determine the

exact nature of the complex or its relation to induction of hepatic porphyria with allylisopropylacetamide.

DISCUSSION

The experiments have shown that ingestion of the barbiturate, allylisopropylacetamide (Sedormid®) was responsible for occurrence of mild hepatic porphyria. At the same time an abnormal highly insoluble non-obstructive bile pigment-porphyrin complex appeared in small biliary ducts. When lead subacetate was ingested along with the barbiturate, despite the production of severe erythropoietic porphyria, the abnormal pigment failed to appear.

It is generally accepted that the barbiturate (AIA) produces hepatic porphyria by enhancing activity of ALA synthetase in the liver.[4-6] It is also generally accepted that lead induces erythropoietic porphyria by inhibiting the activity of at least two enzymes, one (ALA dehydratase) which converts ALA to porphobilinogen, and the other (heme synthesase) converts porphyrin to heme.[7-15] The depletion of hemoglobin by some feedback mechanism also increases ALA production. Hence, a vicious cycle of this kind, as occurred in the group fed lead subacetate, induced excessive production of ALA. Because of the inhibitory action of lead on ALA dehydratase, the ALA could not be converted into porphobilinogen, and it was therefore excreted principally in the urine. The partial block by lead of heme synthesase prevented normal conversion of the porphyrins to heme and this resulted in coproporphyrinemia.

The operation of both of these mechanisms, one due to the barbiturate and the other due to lead, in the same animal produced some evidence of antagonism. We have assumed that excess ALA synthetase activity induced in the liver by the barbiturate would ordinarily be reflected in excess production of porphyrins in the liver in the presence of adequate ALA dehydratase activity. The porphyrins, so produced, would either accumulate locally, be excreted, or be distributed for heme production. In the absence of excess requirement for heme by the liver cells, themselves, it would seem that the excess porphyrin made in the liver would either be excreted into the blood or bile. In either case some would be expected to appear in the urine, and this was found. With such a mechanism in operation, the interference by ingestion of lead may be as follows: Lead normally blocks the action of ALA dehydratase. If such a block occurs in the liver, excess barbiturate-induced ALA synthetase activity would be ineffective in production of porphobilinogen, essential for porphyrin synthesis. Excess ALA would then be disposed of in the same way, as in the lead-poisoned animals, principally by excretion in the urine. Our data are in accord with this interpretation because the average ALA excretion in the urine of the LS group was greater than that of the L group, while the urinary excretion of coproporphyrin III was about the same in the two groups.

There was convincing evidence that the addition of the barbiturate to the lead subacetate diet reduced the incidence of lead-induced renal cortical neoplasms. Further inquiry is being made into this subject with the idea that intracellular heme production by renal tubular lining cells may be modified by tubular transepithelial movement of the porphyrins and their precursors.

The occurrence of this abnormal bile pigment-porphyrin product is perhaps not unique, for a similar product was encountered during a study of the action of some hydrazine compounds.[16] It may be suggested that use of methods described here may prove profitable in a study of so-called "inspissated" bile and the source of changes in physical properties of bile in some instances of idiopathic cholestasis of non-obstructive origin. Finally, it raises the question as to whether the type of enzymatic block described in these experiments may be useful in management of some complications occurring in patients with hepatic porphyria.

REFERENCES

1. Glick D:Ed. *Methods of Biochemical Analysis*. Interscience Publishers, Inc. New York 1960 **8**:247-253

2. David JR, Andelman SL: Urinary delta aminolevulinic acid levels in lead poisoning. Arch Environ Health **15**:53-59, 1967

3. Sveinsson CL, Rimington C, Barnes HD: Complete porphyrin analysis of pathological urines. Scand J Clin Lab Invest **1**:2-11, 1949

4. Schmid R, Schwartz S: Experimental pophyria. III. Hepatic type produced by Sedormid. Proc Soc Exper Biol and Med **81**:685-689, 1952

5. Case JD, Aldrich RA, Neve RA: Sedormid-induced porphyria in the rat. Proc Soc Exper Biol and Med **83**:566-568, 1953

6. Goldberg A: The effect of certain barbiturates on the porphyrin metabolism of rabbits. Biochem J **57**:55-61, 1954

7. Haeger-Aronsen B: Studies on urinary excretion of delta aminolevulinic acid and other haem precursors in lead workers and lead-intoxicated rabbits. Scand J Clin Lab Invest **12**:Suppl. 47, 1960

8. Goldberg A, Ashenbrucker H, Cartwright GE, Wintrobe MM: Studies of the biosynthesis of heme in vitro by avian erythrocytes. Blood **11**:821-833, 1956

9. Labbe RF: An enzyme which catalyzes the insertion of iron into protoporphyrin. Biochem Biophys Acta (AMST) **31**:589-590, 1959

10. Watson CT: The erythrocytes coproporphyrin variation in respect to erythrocytes protoporphyrin and reticulocytes in certain of the anemias. Arch Intern Med **86**:797-809, 1950

11. Kench JE, Gillam AE, Lane RE: Haemopoiesis in lead poisoning. Biochem J **36**:384-388, 1942

12. Granick S, Mauzerall D: The Metabolism of Heme and Chlorophyll. D.M. Greenberg (ed.), Metabolic Pathways, Academic Press, New York, **2**:526-616, 1960

13. Dresel EIB, Falk JE: Studies on the biosynthesis of blood pigments. 3. Haem and porphyrin formation from δ-amino levulinic acid and from porphobilinogen in haemolyzed chicken erythrocytes. Biochem J **63**:80-87, 1956

14. Jandl JH, Inman JK, Simmons RL, Allen PW: Transfer of iron from serum iron binding protein to human reticulocytes. J Clin Invest **38**:161-185, 1959

15. Lichtman HC, Feldman F: In vitro pyrrole and porphyrin synthesis in lead poisoning and iron deficiency J Clin Invest **42**:830-839, 1963

16. Lalich SS: Tissue responses to methylhydrazine sulfate feeding. Path Microbiol **25**:527-536, 1962

THE "NUMB CHIN" AND NEOPLASIA

Arnold D. Scheller, Jr.
Floyd A. Davis
Robert E. Slayton

ABSTRACT. Compression neuropathy of the mental nerve ("numb chin" syndrome) occurred in a young man as the first indication of bony metastasis from an embryonal cell carcinoma of the testis. It is proposed that the snug anatomic relationship of the mental nerve in its relatively long and narrow canal predisposes to such conduction block.

INTRODUCTION

In recent years, it has been noted that a seemingly innocuous numbness and sensory loss on the chin, in the distribution of the mental nerve, can be a sign of metastatic cancer.[1,2] Occasionally this finding appears prior to the diagnosis of neoplasia, though more commonly it is associated with known disease.[2] In this paper, a case report of mental neuropathy or the so-called "numb chin" syndrome[2] is presented with a literature review and new thoughts regarding its patho-physiologic basis.

CASE REPORT

C.B., a 19-year-old white male, underwent a left orchiectomy for embryonal cell carcinoma with teratomatous elements in June, 1972. During anesthesia with good muscle relaxation, an abdominal mass was palpated. Chest roentgenogram, bone scan and Tc99n liver spleen scan were negative, but roentgenograms of the gastrointestinal tract and excretory pyelogram revealed a left upper quadrant mass. After a course of bleomycin in late July, the patient underwent a laparotomy, which revealed a large retroperitoneal mass. After partial surgical resection, radiation therapy was given in early August to reduce the size of the mass.

In early September, while shaving, the patient noticed a numb sensation on the left side of his chin. Examination shortly thereafter revealed a deficit for pain, temperature and touch sensation in the appropriate area supplied by the mental nerve (Fig. 1). Later that month, the patient was treated with dactinomycin and vincristine. Approximately three weeks later, enlarged lymph nodes were noted in the left supraclavicular fossa. Cervical, submaxillary and submental nodes were not enlarged. Bone scan showed evidence of bony metastases in the left mandible (Fig. 2). Plain films and laminograms revealed no evidence of tumor of the mandible and mental foramen (Fig. 3). The sensory symptoms remained unchanged.

From the Section of Oncology and Department of Neurological Sciences, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois

Arnold D. Scheller, B.S., Senior Student, Rush Medical College

Floyd A. Davis, M.D., Associate Attending Physician, Presbyterian-St. Luke's Hospital; Associate Professor of the Neurological Sciences, Rush Medical College

Robert E. Slayton, Senior Attending Physician, Presbyterian-St. Luke's Hospital; Associate Professor of Medicine (Oncology), Rush Medical College

In November, the patient developed hoarseness, and physical examination revealed no movement of the vocal cords with phonation. A 4.5 by 5.5 cm mass was noted in the left lateral neck, and there was a question of a mediastinal mass on chest roentgenogram. In February, 1973, pulmonary metastases were noted on chest roentgenogram, and a 10-day course of mithramycin was given. Later that month, he complained of pain in the posterior thoracic region with involvement and collapse, roentgenographically of the fourth thoracic vertebra (T4) and signs of spinal cord compression. He subsequently underwent a laminectomy from T1 to T4, followed by radiation therapy.

DISCUSSION

Mandibular metastasis and mental neuropathy may be the first evidence for metastatic disease[2] and should not be lightly dismissed in patients with malig-

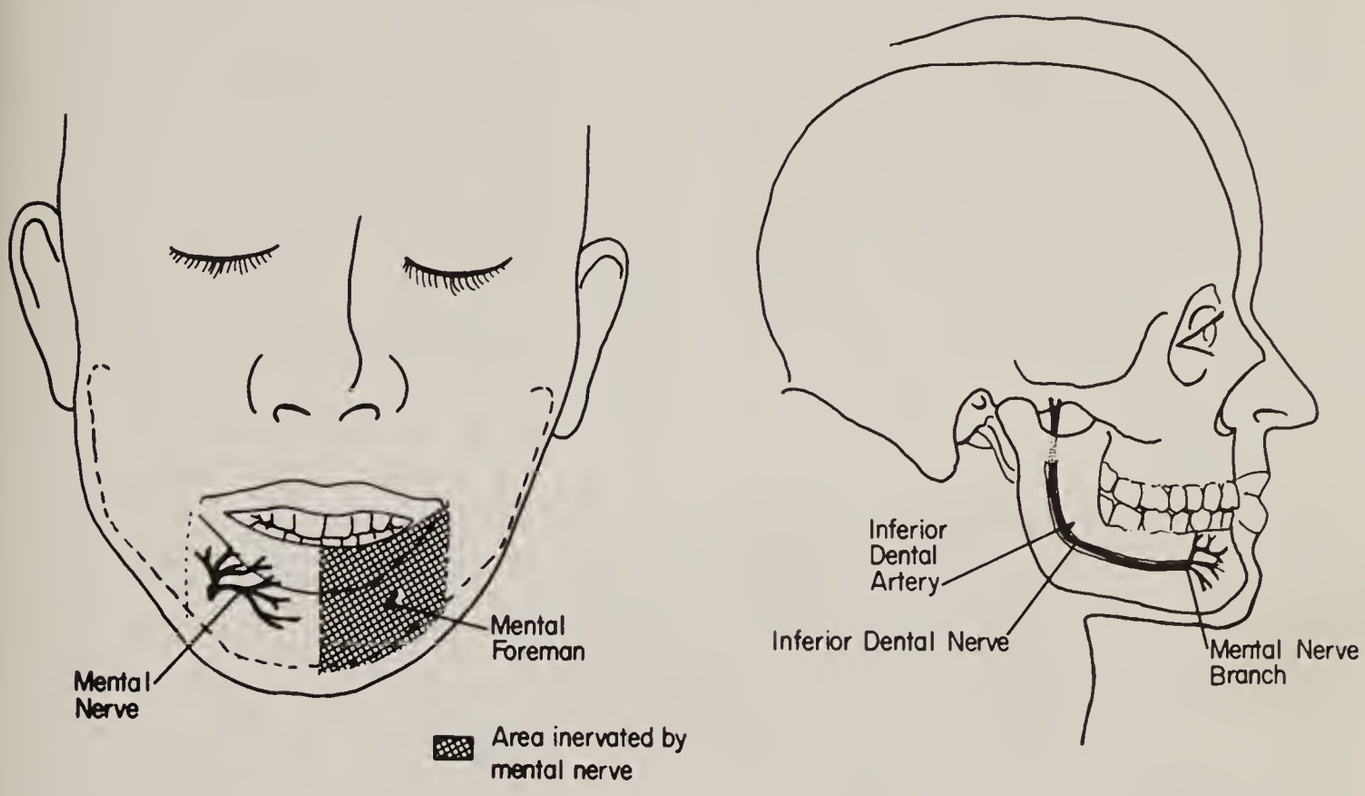


Fig. 1.—(*Left*) Cutaneous innervation of mental nerve (*Right*) Mandibular canal and its contents

Fig. 2.—(*Left*) Normal bone scan, of patient C.B., 7/72 (*Right*) Abnormal bone scan of same patient three months later. Note left mandibular area (arrow)

nancy. Calverley and Mohnac [2] suggested that the syndrome was caused by metastases to the mandible with involvement of the inferior alveolar nerve. Three of their patients had adenocarcinoma of the breast and one had Hodgkin's granuloma. Two of the patients with adenocarcinoma of the breast had pathologic evidence of erosion of one mental foramen. In our case, mental neuropathy did not, by itself, play an important role in clinical management. However, it was the first evidence of bony metastasis and did alert the medical staff to the possibility of widespread bony involvement.

Nobler [1] recognized the unique involvement of the mental nerve in the "numb chin syndrome." He suggested that the neuropathy was caused by pressure from enlarged cervical lymph nodes. He felt it was unique for malignant lymphoma and that the neuropathy could be treated successfully with radiation therapy.

There was no involvement of cervical, submaxillary or submental nodes at any time in this case prior to the neuropathy, nor is there any likelihood that cervical lymph nodes *per se* were related to the mental neuropathy. The canal through which the mental nerve courses does not contain lymphatic elements.[3] The pattern of venous and lymphatic drainage in this area is towards the mucosa of the oral cavity and does not involve the mandibular canal.

The mental nerve is a sensory nerve, and its dysfunction is, of course, represented by sensory signs and symptoms. Typically, as in a complete peripheral nerve lesion, loss of function includes all represented sensory modalities. More practically, one would like to have, at least, combined pin and touch changes (i.e., an absence, diminution or perversion of pin and touch) in the distribution of the mental nerve in order to entertain

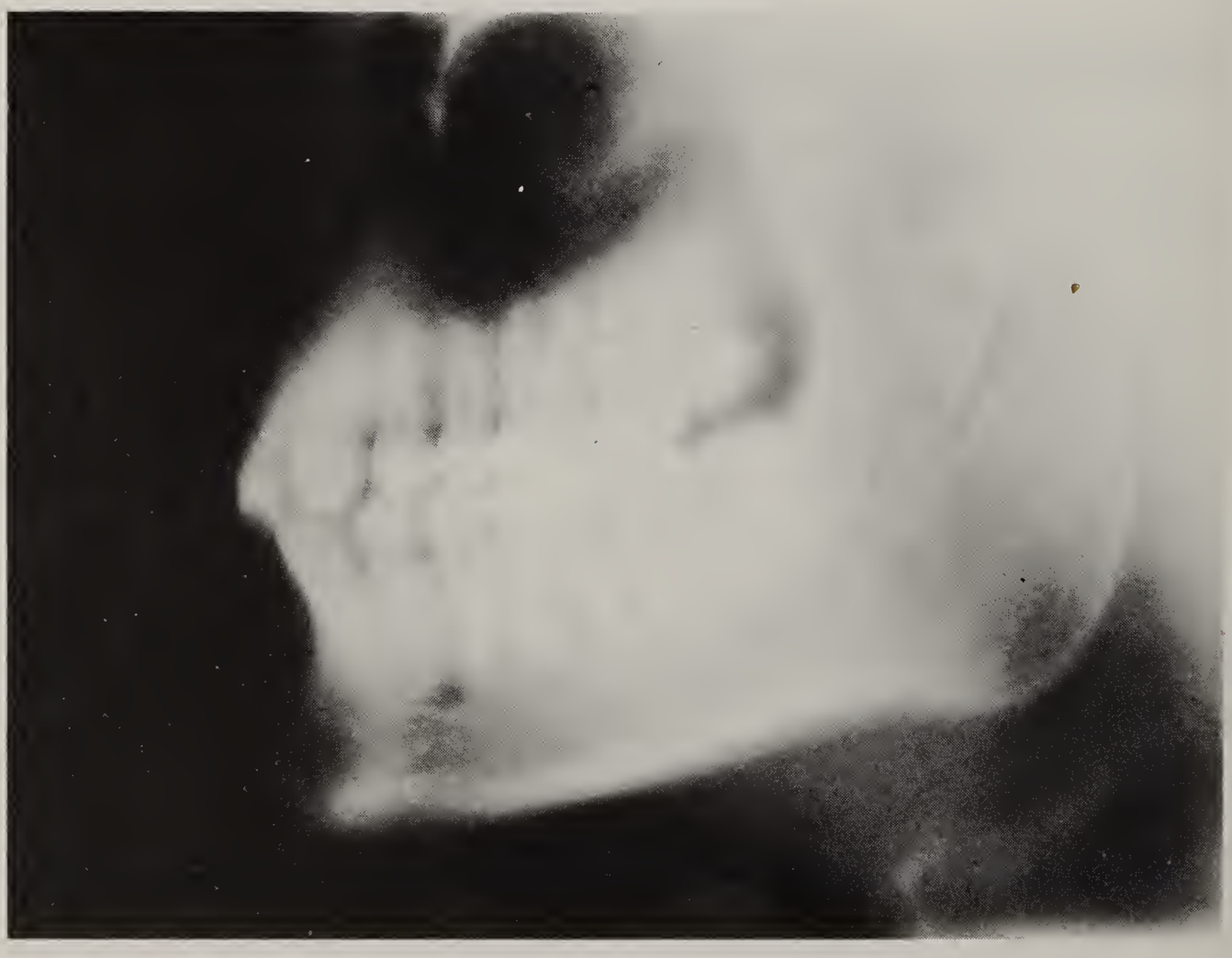


Fig. 3.—Normal tomogram of mental foramen and mandibular canal of patient C.B., 10/72

the diagnosis. A dissociated loss, such as pin sensation only, might conceivably involve central brainstem pathways (descending tract of the trigeminal nerve) rather than a peripheral nerve lesion. Since a small cerebral lesion might conceivably mimic a mental neuropathy, the absence of other cerebral findings and the strict localization of findings in the anatomic distribution of the mental nerve must be emphasized. The mental nerve dysfunction is believed to be due to a direct invasion of the canal.[2] Alternatively, there is no good evidence to indicate that nutritional or so-called non-invasive carcinomatous factors play an important role. There is good reason to suggest that the normal anatomic relationships of the mental nerve are extremely important in the pathogenesis of the condition.

The mandibular canal, which houses the mental nerve, like the facial canal, is one of the longest and narrowest bony tunnels through which a nerve passes. The mental nerve arises in the mandibular canal as a branch of the inferior alveolar nerve and emerges from the mental foramen. It is distributed to the skin of the chin, lower lip, and mucous membrane of the gingivobuccal sulcus, usually stopping at midline, as shown in Fig. 1. Little is known about the normal nerve/canal ratio. Nonetheless, the canal is probably on the "snug" side for its contents. The "snugness" and length of the canal have important implications with respect to the probable pathophysiology.

It is known that localized axonal lesions that do not disrupt the physical continuity of the fiber can destroy the impulse-producing mechanism without blocking conduction. This occurs when the current generated by the action potential (so-called action current) spreads to the other side of the injured region and is strong enough to produce a threshold depolarization. The impulse will in effect, jump over the blocked segment. This is possible because normally there is an excess of action current available for conduction.[4] Because of this action current reserve, or safety factor, at least a 4.5 to 5 mm segment of myelinated nerve trunk must be rendered inexcitable before conduction ceases.[5] It is likely that such a phenomenon can occur in clinical conditions where lesions involve short segments of nerve without disrupting its physical continuity.[6] Because of the mental nerve-mandibular canal relationship, an increase in pressure within the mandibular canal will be expected to be transmitted to a segment of the nerve in excess of the minimum 4.5 to 5 mm distance necessary to block conduction. Whether this pressure change results in direct change to the nerve fiber or indirect changes due to ischemia is of little importance from a clinical standpoint. The essential point is that a block of conduction would ensue, and that the anatomic relationships of the mental nerve would be a predisposing factor.

It is likely that any tumor that metastasized to bone can elicit the neuropathy. It has been described with lymphoma, Hodgkin's disease, and carcinoma of the lung and breast.[1,2] Our patient appears to be the first case associated with an embryonal cell carcinoma of the testis. We have seen six other patients with mental neuropathy. All had adenocarcinoma of the breast with widespread bony metastases. Two of the patients died within a year of the diagnosis of the neuropathy.

ACKNOWLEDGEMENT

The authors wish to express their appreciation for the assistance of Kathleen Scheller in preparation of the manuscript.

REFERENCES

1. Nobler MP: Mental nerve palsy in malignant lymphoma. Cancer **24**:122-127, 1969
2. Calverley JR, Mohnac AM: Syndrome of the numb chin. Arch Int Med **112**:819-821, 1963
3. Brash JC: *Cunningham's Textbook of Anatomy*, 9th ed. London, Oxford University Press, 1951, pp. 1026-1029.
4. Tasaki I: *Nervous Transmission*. Springfield, Illinois, Charles C Thomas Publishers, 1953, p. 164
5. Hodgkin AL: Evidence for electrical transmission in nerve. J Physiol (London) **90**:211, 1937
6. Davis FA, Jacobson SG: Altered thermal sensitivity in injured and demyelinated nerve. J Neurol Neurosurg Psychiat **34**:551, 1971

METASTATIC CARCINOMA FROM THE CERVIX TO THE CALCANEUS: A CASE REPORT

Allan N. Levine
Mitchell B. Sheinkop

Abstract. A rare metastatic squamous cell carcinoma in a calcaneus has been documented in a 72-year-old woman whose squamous cell cancer of the cervix was irradiated five months previously. Radiography and technetium bone scan preceded the crucial bone biopsy. The importance of exact tissue diagnosis is stressed.

INTRODUCTION

The orthopaedic surgeon is all too frequently confronted with a lytic lesion of unknown etiology in bone. The age of the patient, location of the lesion, and the radiological appearance may suggest a diagnosis; however, histologic substantiation is mandatory. The pathologist becomes the final diagnostician, and an adequate tissue specimen must be received to arrive at the ultimate diagnosis. Since the survival statistics and methods of treatment differ according to the site of the primary carcinoma, it is of tantamount importance that treatment is not begun until a tissue diagnosis can be made.

The purpose of this presentation is to demonstrate a metastatic site from a primary tumor that uncommonly affects bone.

From the Department of Orthopaedic Surgery, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois and the Section of Orthopaedic Surgery, University of Chicago, Chicago, Illinois

Allan N. Levine, M.D., Resident, Section of Orthopaedic Surgery, University of Chicago, Chicago, Illinois

Mitchell B. Sheinkop, M.D., Attending Physician and Chief, Pediatric Orthopaedic Clinic, Presbyterian-St. Luke's Hospital; Assistant Professor, Rush Medical College, Chicago, Illinois

CASE REPORT

W.H., a 72-year-old, black female, was referred to the Orthopaedic Department of the University of Chicago Hospitals and Clinics on November 29, 1972, with the chief complaint of pain and swelling of the right heel and ankle coming on spontaneously in the previous three-to-four weeks. Five months prior to admission, the patient had completed "radical radiation therapy" (total tumor dose—7,000 rads) for treatment of "Stage III squamous cell carcinoma of the cervix." Physical examination revealed a well-developed, well-nourished, black female in distress secondary to pain in her right heel. Pertinent findings included a large, firm, non-tender uterus and a tender, nonerythematous, firm swelling 2x3 cm along the lateral border of the right calcaneus. Tenderness was most marked upon deep palpation of the superior-posterior border of the calcaneus.

Laboratory studies of the blood were all within normal limits, including serum calcium, phosphorous, alkaline phosphatase, and protein electrophoresis. On radiographs, there was osteopenia of all bones of the right foot and ankle, with several discrete radiolucent areas in the calcaneus and destruction of the cortex in its superior-posterior margin (Fig. 1). Technetium polyphosphate bone scan revealed an area of equivocal activity in the left iliac crest (Fig. 2) and marked

Fig. 1-A & B—Radiography of right foot and ankle revealing discrete lytic areas in calcaneus and destruction of cortex in superior-posterior border in lateral view.

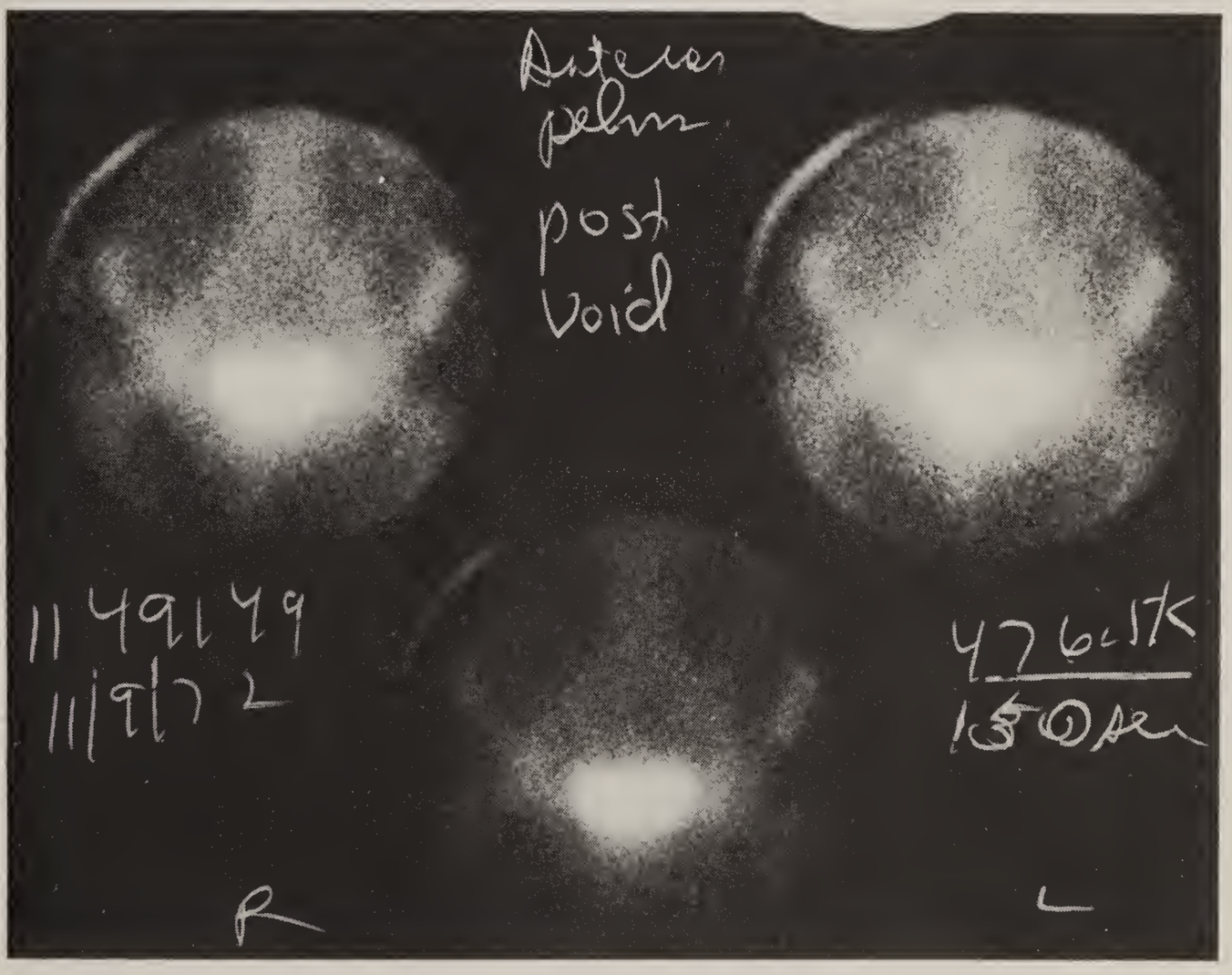


Fig. 2—Technetium polyphosphate bone scan of pelvis showing area of slightly increased activity in left iliac crest.

increased activity in the right calcaneus (Fig. 3)

An open wedge biopsy and curettage was performed. The pathologic diagnosis was made of metastatic squamous cell carcinoma of similar cell type to the cervical biopsy taken five months previously (Figs. 4a & b). The patient sub-

Fig. 3—Technetium polyphosphate scan of both feet showing marked increased activity in right calcaneus.

Fig. 4-A—Metastatic well differentiated squamous cell carcinoma from right calcaneus showing epithelial pearl and of similar cell type to Fig. 4-B.

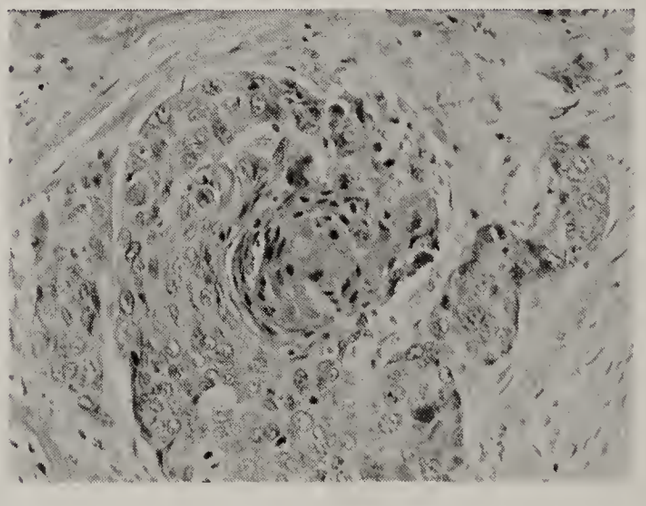


Fig. 4-B—Biopsy of cervix.

sequently received a total of 3500 rads directed to the right heel and has had partial relief of pain.

DISCUSSION

Greater than 75 percent of osseous metastases are from breast, prostate, lung, thyroid, and kidney.[2] The least likely primary sites to metastasize to bone are: rectosigmoid—5 percent; pancreas—6 percent; cervix—9 percent; and stomach—9.5 percent.[1,5] Acral metastasis (below the knees or elbows) is quite rare, and half of these are from lung carcinoma.[1-4] The bones of the feet are involved more frequently than those of the hands, and the specific bones usually affected are the terminal phalanges.[3] To our knowledge, no case of cervical carcinoma with metastasis to the tarsal bones has been previously reported.

ACKNOWLEDGEMENT

Acknowledgement is made to Dr. Phillip W. Graff, Associate Professor, Department of Pathology, University of Chicago Hospitals and Clinics, for his assistance.

REFERENCES

1. Johnston AD: Pathology of metastatic tumors in bone. Clin Orthop **73**:8, 1970

2. Lodwick GS: The radiologic diagnosis of metastatic carcinoma in bone. In *Tumors of Bone and Soft Tissue*, University of Texas, MD Anderson Hospital and Tumor Institute. Chicago, Yearbook Medical Publishers, 1965, pp. 253-268

3. Mulvey RB: Peripheral bone metastasis. Am J. Roentgen **91**:155, 1964

4. Sutherland CG, Decker FH, Cilley EL: Metastatic malignant lesions in bone. Am J Cancer **16**:1457, 1932

5. Warren S: In *Textbook of Pathology*, Anderson WD, 5th ed. St. Louis, CV Mosby Co, 1966, p. 408

ABSTRACTS

OF PUBLICATIONS BY THE STAFF

Biochemistry

Booyse F, Kisieleski D, Seeler R, Rafelson M Jr: Possible thrombosthenin defect in Glanzmann's thrombasthenia. *Blood 39:377, 1972*

Microquantitation of thrombosthenin by single radial immunodiffusion in conjunction with a specific immunohistochemical antibody staining technique has indicated an immunologic defect or absence of the surface-localized thrombosthenin (S-thrombosthenin) in platelets from Glanzmann's thrombasthenic patients. In addition, ADP- and ATP-induced changes of the surface of normal platelets could not be demonstrated with Glanzmann's thrombasthenic platelets.

Biomechanics

Apter JT, Mason P: Dynamic mechanical properties of mammalian ureteral muscle. *Amer J Physiol 221:266, 1971*

This study gives a description and measurements of the mechanical properties of ureters isolated from anesthetized dogs and calves, in particular the stress response to step-function and sinusoidally oscillating strains. A step-function extension strain of a strip of the ureter was accompanied by a sharp rise in stress which fell along an essentially exponential course (stress relaxation) to be followed by a single or by repeated recontractions, depending on temperature, ionic environment, and strain level. A sinusoidally oscillating strain was accompanied by an oscillating stress which sometimes led (as for inert visco-elastic material) and sometimes lagged (as for muscle) behind the strain, depending on the oscillation frequency. In addition, the stress, though oscillating, was nonlinear since it was not sinusoidal except for very small strains and at frequencies higher than .8 Hz. Quantification of these data as system parameters was accomplished by referring to a simplified, idealized physical system which responds to similar strains with similar stress behavior; that is, with recontraction, phase leads, phage lags, and nonlinearities, thus strongly resembling ureteral specimens.

Endocrinology and Metabolism

Garland JT, Daughaday WH: Feedback inhibition of pituitary growth hormone in rats infected with *Spirometra mansonoides*. *Proc Soc Exper Biol Med 139:497, 1972*

Spirometra mansonoides spargana produce a potent "worm factor" that causes both the generation of somatomedin and linear growth in hypophysectomized rats without detectable immunoassayable rat growth hormone (RGH). Implantation of these spargana has no significant effect on the growth of normal rats but did cause a 34 percent decrease in pituitary weight ($p < .001$) and a 68 percent decrease ($P < .001$) in pituitary RGH content. Hemipituitaries removed from these rats released a normal proportion of their RGH during a control incubation and responded with an appropriate increase during stimulation by high potassium. Either the "worm factor" has growth hormone-like action on the hypothalamus or pituitary, or somatomedin itself plays an important role in the feedback regulation of pituitary growth hormone.

Ryan WG, Schwartz TB, Northrop G: Treatment of Paget's disease with mithramycin: Further experiences. *Seminars Drug Treat 2:57, 1972*

The results of treatment in fifty patients with Paget's disease of bone are described and confirm and extend our previously reported observations that mithramycin is an effective form of therapy for this disease. Mithramycin in a dose of 15 to 25 micrograms per kilogram per day as 24-hour infusions for ten days produced a reduction in serum alkaline phosphatase averaging 62 percent and acutely reduced urinary hydroxyproline to normal or near normal in all patients studied. These biochemical parameters were accompanied by subjective symptomatic relief of headaches and bone pain, greater mobility of the joints involved and, in one patient, apparent decompression of the spinal cord. Radiographically demonstrable improvement in bone architecture has been observed in two patients 18 to 24 months following therapy. Bone biopsies immediately pre- and post-treatment have shown marked reduction in numbers of osteoclasts and osteoblasts.

Mithramycin was also useful in reducing serum alkaline phosphatase as well as in giving symptomatic relief to ten outpatients treated by bolus intravenous injections of 15 micrograms per kilogram, five days a week for four weeks. With careful monitoring, the known adverse effects of mithramycin have been minimized. Significant hepatic toxicity has not resulted, minimal renal toxicity has been encountered, and in no patient has a bleeding episode occurred. These observations indicate that mithramycin is an effective and safe treatment for Paget's disease of bone.

Hematology

Fried W, Gregory SA, Knospe WH, Trobaugh FE Jr: Regulation of plasma erythropoietin levels in mice with impaired responsiveness to erythropoietin. *J Lab Clin Med 78:449, 1971*

Plasma erythropoietin (Ep) levels of WWv mice are higher than those of comparably anemic nonmutants (++). This difference is no longer present seven days after transplanting 2 x 10^5 ++ marrow cells into WWv mice. At this time, the response of WWv mice to Ep is comparable to that of ++'s; yet the colonizing ability of their hematopoietic cells is still defective. This difference in the plasma Ep level of WWv and of ++ mice is not associated with differences in the Po_2-50 of their hemoglobin, or in the rate at which the Ep is cleared from their plasma. These studies suggest that in WWv mice, the rate of Ep production at any level of anemia is modified by the ability of the hematopoietic cells to respond to Ep. The mechanism by which the Ep responsiveness affects the Ep production is unclear. Observations in man have also indicated that the plasma Ep level of patients with an active erythropoiesis is lower than of comparably anemic patients with a suppression of erythropoiesis. Perhaps in man also, the level of erythropoiesis modulates the rate of the Ep production in response to anemia.

Fried W, Knospe WH, Trobaugh FE Jr: Effect of differentiated myeloid cells on hematopoietic stem cell (HSC) proliferation. *Proc Amer Soc Clin Invest 64th Ann Mtg, 1972, p. 33a*

Previous studies showed that HSC transplanted into mice given cytoxan four days before x-irradiation regenerate faster than those in mice which were only irradiated. The factors responsible for this enhancement of HSC replication were studied. Five mg of cytoxan was injected into CF_1 mice, and controls received saline. One to ten days afterward they received 1000 R x-irradiation and 10^6 marrow cells. HSC in their femoral marrow were assayed at various times afterward by the spleen colony method of Till and McCulloch. Injection of cytoxan four days before x-irradiation significantly enhanced regeneration of transplanted HSC, whereas injection seven days before resulted in a significant delay of HSC regeneration. The number of HSC and nucleated marrow cells were determined, and differential cell

counts were done one hour after x-irradiation on femoral marrow cells of mice which received saline or cytoxan four or seven days before x-irradiation. The nucleated cell count, number of HSC, and number of differentiated cells of mice given cytoxan four days before radiation were less than in controls which received saline only. In those treated seven days preradiation, the number of HSC remained less than control, the nucleated cell count was no different from control, but differentiated cell counts revealed 85 percent of the marrow cells to be differentiated myeloid cells (bands and segs) as compared to <50 percent in the control group. These results suggest the conclusion that the proliferation of hematopoietic stem cells is modulated by cell: cell interactions with mature myeloid elements in the milieu.

Fried W, Knospe WH, Trobaugh FE Jr: Effect of sex differences on extrarenal erythropoietin production. *Proc Soc Exp Biol Med 137:255, 1971*

Evidence is presented to show that extrarenal as well as renal sites of Ep production are more sensitive to hypoxia in male than in female rates. However, on exposure to very intense hypoxia, the peak plasma Ep levels of both anephric and intact female rats are comparable to those of males.

Knospe WH: Effect of fetuin and other alpha globulins on cellular proliferation. *Blood 38:818, 1971*

Fetuin, a globulin from fetal calf serum, accelerates the recovery of hematopoietic stem cells in sublethally irradiated mice. Normal human plasma, containing a comparable amount of protein, had no such effect. An extract prepared from homogenized mouse spleen had a similar but lesser effect. Fetuin and other alpha globulins may have a physiologic role in cellular proliferation.

Knospe WH, Blom J, Goldstein HB, Crosby WH, Davis M: Delayed bone marrow aplasia in rats protected against lethal irradiation by allogeneic marrow transplantation. *Radiat Res 47:199, 1971*

Rats receiving lethal whole-body irradiation were protected with allogeneic bone marrow grafts. In 37 percent of late survivors, a mild and atypical form of secondary disease occurred with marrow aplasia as the major manifestation. Marrow aplasia was associated with extensive damage to the sinusoidal microcirculation which coexisted with histologic evidence of a graft-versus-host reaction in the spleen. It is possible that immune damage to the microcirculation was the cause of the marrow aplasia. The transplantation of allogeneic bone marrow in irradiated animals may be complicated by marrow aplasia.

Sutton DMC, Hauser R, Kulapongs P, Bachmann F: Intravascular coagulation in *abruptio placentae*. *Amer J Obstet Gynec 109:604, 1971*

Sequential coagulation profiles were performed in a series of 17 consecutive patients with *abruptio placentae*. These patients were divided into three groups on the basis of the fibrinogen concentration and the severity of coagulation defects. Group A consisted of seven patients with no obvious coagulation disturbance and fibrinogen concentrations comparable to those found in normal women at term. Statistical analysis, however, revealed a significantly decreased mean level of factor VIII and a prolonged Clauss fibrinogen time. Group B consisted of five patients with fibrinogen concentrations between 200 and 300 mg percent and clearly disturbed coagulation profiles characterized by decreased levels of factors V, VIII, and XIII and by the presence of circulating fibrin-split products. Group C consisted

of the five most severely affected patients. The concentrations of fibrinogen and factor V were lower than those in Group B. In addition, these patients differed from Group B in that the vitamin K-dependent factors II and X were decreased. Clinical severity and extent of bleeding increased from Group A through Group C. Tests for increased systemic fibrinolysis were, in general, negative. This result and the occurrence of severe deficiencies of fibrinogen and other clotting factors, which cannot be explained on the basis of blood loss alone, indicate that the coagulation disturbance was caused by consumption coagulopathy. Evacuation of the uterus resulted in prompt improvement in all patients.

Immunology

Williams RC Jr, Gewurz H, Quie PG: Effects of fraction I from *Yersinia pestis* on phagocytosis *in vitro*. *J Infect Dis 126:235, 1972*

Fraction I, obtained from capsular material of *Yershinia pestis* (formerly *Pasteurella pestis*) was studied for its effect on *in-vitro* phagocytosis. No impairment in phagocytic systems employing leukocytes from men or rabbits plus several different test strains of (*Staphylococcus, Streptococcus, and Proteus*) bacteria was noted if opsonic activity was primarily dependent on γG opsonin. However, distinct interference with heat-labile components of serum participating in opsonization of gram-negative organisms such as *Escherichia coli* was noted. Fraction I activated the complement system, particularly affecting C′4 and C′2, and, in concentrations of 200 μg/ml of fresh human serum, it produced consumption of 40 percent of the total hemolytic activity of complement. Blocking of heat-labile opsonins by Fraction I, particularly for such organisms as *E. coli*, seems to be associated with its interaction with and partial activation of the complement system.

Edwards LD, Levin S, Lepper MH: A comprehensive surveillance system of infections and antimicrobials used at Presbyterian-St. Luke's Hospital, Chicago. *Amer J Public Health 62:1053, 1972*

The surveillance system at Presbyterian-St. Luke's Hospital includes all patients with community and/or hospital onset infections and those who received antimicrobials during their hospital stay.

Numerator data is collected by three nurse epidemiologists who visit all hospital units two to three times per week. Charts are selected for review on the basis of initial screening of temperature sheets, procedural and medication indices which are separate from the patients' charts and a daily review of bacteriological reports in the laboratory. Data collected from January 1967 through June 1970 revealed a nosocomial infection rate of 7.2 percent of patients and a community onset infection rate of 8.5 percent of patients; 20.4 percent of patients received antimicrobials.

Five computerized monthly reports related to interrelationships of antimicrobial usage, hospital onset infection, operative procedures and hospital services are utilized. Additional reports are utilized for epidemiologic research.

The cost of initial development of this system was 32¢ per patient per day, for continued development, 23¢, and for maintenance, 16¢ per patient per day.

Glick N, Levin S, Nelson K: Recurrent pulmonary infarction in adult chickenpox pneumonia. *JAMA 222:173, 1972*

The diagnosis of repeated pulmonary emboli was made for a 32-year-old man with chickenpox pneumonia. This case and previously reported cases emphasize that upon recognition, the treatment of pulmonary emboli occurring with chickenpox pneumonia may be the only specific therapy which can be offered to these often critically ill patients.

Levin S, Balagtas R, Susmano A, Edwards L, Dainauskas J: Meningococcus endocarditis at the site of Starr-Edwards mitral prosthesis. *Arch Intern Med 129:963, 1972*

To our knowledge, there has been no prior report of meningococcal endocarditis involving a Starr-Edwards mitral prosthesis. A fulminant course ending in meningitis and rapid death is quite characteristic of chronic meningococcal septicemia and may suddenly terminate a mild apparently slowly progressive course.

Nelson KE, Levin S, Spies HW, Lepper MH: Treatment of *Hemophilus influenzae* meningitis: A comparison of chloramphenical and tetracycline. *J Infect Dis 125:459, 1972*

A study was done to compare the efficacy of chloramphenical and tetracycline for the treatment of meningitis due to *Hemophilus influenzae*. Alternate patients with this disease were treated with one or the other of these drugs given in daily doses of 50 mg/kg at intervals by the intravenous route. In 325 patients studied, no significant differences between the two groups could be detected with respect to rates of mortality and acute complications, speed of defervescence, or rapidity of clinical recovery. Although ampicillin is the best single drug for the initial treatment of bacterial meningitis because of its broad efficacy and relative nontoxicity, our data suggest that either chloramphenicol or tetracycline could also be used for the treatment of meningitis due to *H. influenzae* when ampicillin is contraindicated because of allergic reactions or drug failure, or for other reasons.

Rafoth R, Morse R, Edwards LD, Jupa J, Levin S: Tuberculous peritonitis after laparotomy. *Scand J Infect Dis 4:139, 1972*

Four cases are described of tuberculous peritonitis occurring six to ten weeks following laparotomy for unrelated illnesses. Four similar cases from 16 previously reported series of tuberculous peritonitis are also described. The possibility of mechanical activation of old peritoneal or mesenteric granulomas is considered. An incubation period of four to ten weeks from surgery to onset of symptoms or diagnosis is suggested in seven of eight reported cases.

Medicine

Klinger AD, Perez A: Anticoagulants in sickle cell disease. *JAMA 64:200, 1972*

1. Anticoagulants seem to help prevent the pain of sickle cell crises.
2. There is some clinical evidence that continuous use of anticoagulants may not be necessary but that its intermittent use is helpful.
3. Anticoagulants appear of little value once bone pains have begun.
4. Antibiotics used alone or with anticoagulants appear to shorten the period of pain or, in some instances, even abort the pain before it has completely incapacitated the patient.
5. The number of bone crises in individuals having homozygous S or S-thalassemia varies considerably. Those with homozygous S have a great tendency for them, while those with S-thalassemia have mild-to-considerable pain.
6. The reasons for discrepancies in individual response to bone crises or the number of crises experienced are not obvious at this time. Some people with S disease have a remarkable capacity for work despite painful crises. Some evidence exists that anticoagulants, analgesics and probably antibiotics enhance this capacity. We cannot help but be impressed with the work motivation of these people.

7. The role of birth control pills, menstruation, and ASA is not clear; but ASA may be efficacious in some instances.

8. Elective surgical procedures requiring general or spinal anesthesia probably should be eschewed in those with the homozygous form of the disease.

9. In our opinion, drugs offer only palliation in the above conditions. Eradication of the disease through genetic counseling is preferable.

Microbiology

Falk LA, Wolfe, LG, Deinhardt F: Isolation of *Herpesvirus saimiri* from blood of squirrel monkeys (*Saimiri sciureus*). *J Nat Cancer Inst 48:1499, 1972*

Virus was isolated from 11 of 13 blood samples obtained from healthy squirrel monkeys (*Saimiri sciureus*); these isolates were antigenically similar, if not identical, to *Herpesvirus saimiri* (HVS). By co-cultivation with vero cells, virus was isolated from both whole blood and lymphocytes separated from whole blood on Ficoll-Hypaque (FH) gradients. Attempts to isolate virus from FH cell pellets (erythrocytes and polymorphonuclear leukocytes) or cell-free extracts of whole blood, lymphocytes, or cell pellets failed. The squirrel monkey isolates were neutralized or reacted positively in immunofluorescence tests with anti-HVS sera but not with antisera to herpes simplex virus or *Herpesvirus platyrrhinae*. Cotton-topped (*Saguinus oedipus*) and white-lipped (*S. fuscicollis* and *S. nigricollis*) marmosets, experimentally infected with one isolate, developed a lympho-proliferative disease and survived 18 to 26 days post-inoculation. Macroscopic and microscopic features of the neoplastic disease were indistinguishable from those produced by the prototype strain of HVS.

Johnson TR, Massey RJ, Deinhardt F: Lymphocyte and antibody cytotoxicity to tumor cells measured by a micro-^{51} chromium release assay. *Immun Comm 1:247, 1972*

^{51}Chromium release micro-assays for both lymphocyte and antibody cytotoxicity have been developed. Tests vs. several different types of target cells can be performed on one to five ml of blood. The results are objective, highly reproducible and can be obtained within six hours. Application of this test system to primates carrying tumors induced by various onco-RNA viruses has shown highly specific responses, i.e., the animals developed lymphocyte and antibody cytotoxicity against cells transformed by the same virus which had induced their tumors but they remained non-reactive against cells transformed by other viruses.

Northrop RL, Gardner WM, Geittmann WF: Rubella reinfection during early pregnancy: A case report. *Obstet Gynec 39:524, 1972.*

A woman in the seventh week of pregnancy developed a rash and arthritis, and rubella was diagnosed. A rubella HI antibody titer of 20 was detected in the IgG of a blood sample obtained at that time. During the next two weeks, the serum HI antibody titer increased eightfold. Rubella virus was isolated from the products of conception obtained after a therapeutic abortion. These findings suggested that viremia and generalized infection, including intrauterine infection, can occur in reinfection with rubella.

Wolfe LG, Ogden JD, Deinhardt JB, Fisher L, Deinhardt F: Breeding and hand-rearing marmosets for viral oncogenesis studies. In *Breeding Primates*, Basel, *S. Karger, 1972, pp. 145-157*

The care, maintenance and performance of the marmoset breeding colony and hand-rearing operation in our laboratory were summarized for a three-year period, 1968 through

1970. During this period 105 wild-caught breeding pairs of white-lipped or cotton-topped marmosets yielded 357 deliveries. The 357 deliveries produced 671 offspring, approximately 85 percent of which were live births. Of the six species or subspecies represented, *S. fuscicollis illigeri* proved to be the best producers. Parent-reared and hand-reared colony-born marmosets also bred and reproduced in our laboratory; 14 of 36 of the second generation, and three of four of the third generation animals survived longer than 30 days. The poor performance of primiparous colony-born marmosets, compared to primiparous wild-caught animals and all multiparous females, was responsible for the low survival rate of the second generation marmosets. The advantages of hand-rearing versus parent-rearing were discussed, including the significant effect of hand-rearing on reduction of interbirth intervals. The survival rate of 361 hand-reared marmosets was comparable to parent-reared animals. The value of colony-born marmosets for viral oncogenesis studies is briefly discussed.

Wolfe LG, Smith RK, Deinhardt F: Brief communication: Simian sarcoma virus, Type 1 (*Lagothrix*): Focus assay and demonstration of nontransforming associated virus. *J Nat Cancer Inst 48:1905, 1972*

The focal transformation of marmoset lung cells by simiam sarcoma virus, Type 1 (SSV-1) was quantitative without an agar overlay required. Pretreatment of the indicator cells with diethylaminoethyl-dextran increased the sensitivity 10 to 50 times. A 10- to 100-fold excess of nontransforming associated virus (SSAV-1) was demonstrated in SSV-1 stocks by interference tests and electron microscopy. SSV-1 produced by transformed marmoset, human, or cat cells retained its oncogenicity for marmosets.

Wolfe LG, Smith RD, Hoekstra J, Marczynska B, Smith RK, McDonald R, Northrop RL, Deinhardt F: Oncogenicity of feline fibrosarcoma viruses in marmoset monkeys: Pathologic, virologic, and immunologic findings. *J Nat Cancer Inst 49:519, 1972*

Two strains of feline fibrosarcoma virus, Snyder-Theilen (ST-FeSV) and Gardner-Arnstein (GA-FeSV), consistently induced undifferentiated sarcomas or fibrosarcomas in marmoset monkeys, *Saguinus fuscicollis*, *S. nigricollis*, and *S. oedipus*. The invasive neoplastic disease was characterized by a progressive course and death one to six months after inoculation. Metastases to lung and regional lymph nodes were observed in 20 percent of the animals. Sarcomas induced by cell-free virus (primary tumors) contained group-specific (gs) antigen but no demonstrable C-type virus; complete infectious virions were produced after these tissues were explanted *in vitro* or were inoculated into susceptible hosts *in vivo*. Cell lines established both from primary and serially transmitted tumors produced C-type virus that was oncogenic in marmosets and cats. The serially transmitted marmoset tumors, composed primarily of recipient cells, contained C-type virus, and a cell-free extract of one of these tumors induced transformation of cat embryo cells *in vitro*. Gs antibodies were detected in the serum of 70 percent of the tumor-bearing marmosets that had post-inoculation courses of six weeks or longer.

Pathology

Hindo WA, Clasen RA, Rayudu GVS, Pandolfi S: Technetium in cryogenic cerebral injury and edema. *Arch Neurol 27:526, 1972*

The distribution of technetium given as the pertechnetate ion and as the diethylenetriaminepentacetic acid chelate was studied in the brains of dogs with cryogenic lesions. There

was more of the chelate than the free form in the necrotic lesion. The radioactivity of the tissue, four hours after injection of the isotope, was compared to the values at 15 minutes. The greatest increase in radioactivity was found in the edema fluid but the concentration of the isotope in both forms was significantly less than that in the serum. The experimental model was then compared to human disease. It was concluded that a scan at four hours should be superior to a 15-minute scan and that a careful comparison of early and late scans could give a quantitative measure of the edema surrounding brain tumors.

Psychiatry

Garron DC, Molander L, Cronholm B, Lindsten J: An explanation of the apparently increased incidence of moderate mental retardation in Turner's syndrome. *Behav Genet 3:37, 1973*

The distributions of scores achieved by 44 persons with Turner's syndrome on two tests of intelligence are analyzed. Bimodal trends in these distributions are attributed to the effect on the Full Scale IQ of lower scores on specific, nonverbal subtests. Therefore, the diagnosis of Turner's syndrome does not imply an increased risk of a general if moderate intellectual retardation but does indicate a need for careful evaluation of the range of abilities in affected persons.

Leavitt F, Garron DC: Choice of association by schizophrenics as a function of probability. *J Consult Clin Psychol 38:439, 1972*

Choice of association among schizophrenics was studied, using a complex probability-learning paradigm. An 80:20 and 60:40 probability ratio was used to establish two response hierarchies simultaneously. Only the 60:40 ratio discriminated the schizophrenics from the normals. In this condition, the schizophrenics chose the primary association significantly more often than the normals. There are at least two interpretations possible: (a) Schizophrenics differ from normals on associative chains lacking a strong primary association and respond by overemphasizing small differences; or (b) schizophrenics are less sensitive to exact probability cues than normals and adopt arbitrary response ratios that recognize that one association is more probable than the other. These findings pose problems for W. E. Broen, Jr.'s, and L. H. Storms', and S. A. Mednick's conceptions of schizophrenia. Support for L. J. Chapman's position is discussed.

Radiology

Sondag TJ, Petasnick JP, Patel SK, Alcorn FS: Hypernephromas with parasitic blood supply derived from the superior and inferior mesenteric arteries. *Radiology 103:509, 1972*

Three cases of hypernephroma in which the tumor blood supply was obtained from the inferior or superior mesenteric artery are presented. In each case, the origin of the blood supply was demonstrated by selective arteriography. Correlation of arteriographic and surgical findings indicates that the demonstration of parasitic blood supply from the mesenteric arteries is a reliable sign that the hypernephroma has extended beyond the renal capsules and has invaded the mesentery of the colon.

Renal and Nutrition

Kovithavongs T, Becker FO, Ing TS: Parathyroid hyperfunction in acute renal failure. *Nephron 4:254, 1972*

Serial serum parathyroid hormone values were determined in four patients with acute renal failure. They were found to be moderately elevated and in general correlated with hypocalcemia.

Surgery

Gilchrist RK: The postmastectomy massive arm: A usually preventable catastrophy. *Amer J Surg 122:363, 1971*

To summarize, full and complete motion of the arm and shoulder should be obtained during the hospital stay. Patient education as to dependent lymph drainage and prevention and treatment of skin injuries is part of a surgeon's responsibility. Thumb pressure applied repeatedly to break up lymph pooling in the subcutaneous tissues must be taught and checked by the doctor supervising the patient. Such a program will prevent the development of appreciable arm swelling and will result in marked regression in most cases.

Najafi H, Lal R, Khalilli M, Serry C, Rogers A, Haklin M: Left ventricular hemorrhagic necrosis: Experimental production and pathogenesis. *Ann Thorac Surg 12:400, 1971*

Left ventricular subendocardial hemorrhagic necrosis, a lesion different from myocardial infarction, has been considered a major cause of death in patients undergoing operation for valvular heart disease. To determine its pathogenesis, calves were placed on bypass, and the myocardium was challenged by the unphysiological circumstances usually existing in clinical open-heart surgery. These consisted of total ischemia, total oxygenation (with equal or unequal pressures in the coronary vessels), and perfusion of one or different combinations of two coronary branches.

Total and even myocardial oxygenation and total ischemia up to one hour were associated with minimal myocardial injury and no mortality, while uneven coronary perfusion, especially of an area of complete ischemia in the domain of the left coronary artery, was associated with significant myocardial damage resulting in a high mortality. The pitfalls and shortcomings of extracorporeal coronary perfusion are discussed along with certain hypotheses pertaining to the pathogenesis of the lesion in man.

Pemberton LB, Diffenbaugh WF, Strohl EL: The surgical significance of carcinoma of the gallbladder. *Amer J Surg 122:381, 1971*

The courses of forty-one patients with carcinoma of the gall bladder from 1959 to 1969 were reviewed, and these cases were added to the fifty-nine that had previously been reported. Eight of these 100 patients survived more than two years, six within the last decade. Only five patients had a correct preoperative diagnosis. Respiratory failure was the usual cause of death in our recent group of patients. Early cholecystectomy for cholelithiasis may account for increased salvage in recent patients. Although radical surgical extirpation is not recommended, limited wedge resection of the liver and excision of biliary lymph nodes may have some merit.

Willerson D Jr, Rieckmann KH, Kass L, Carson PE, Frischer H, Bowman JE: The chemoprophylactic use of diformyl diaminodiphenyl sulfone (DFD) in falciparum malaria. *Amer J Trop Med 21:138,1972*

The need for adequate protection against chloroquine-resistant malaria led to the evaluation of diformyl diaminodiphenyl sulfone (DFD) as a chemoprophylactic agent. In this study the prophylactic value of weekly DFD (400 mg) and chloroquine (300 mg) against a chloroquine-resistant strain of *Plasmodium falciparum* is compared with that of two other commonly used regimens which require daily administration of 2,4′-diaminodiphenylsulfone (DDS) dapsone. Protection against mosquito-induced infections was achieved in five of eight volunteers who received weekly DFD and chloroquine, six of eight who received daily DDS (25 mg) and weekly chloroquine (300 mg), and seven of eight who received daily DDS (25 mg) and weekly chloroquine (300 mg) and primaquine (45 mg).

SUGGESTIONS TO AUTHORS

Manuscripts. Manuscripts should be typewritten and double-spaced throughout, including tables, captions, references, etc. The title should be typed all in capitals and begin at the normal lefthand margin of Page 1, running across the entire page, with continuation on next line, if necessary. Authors' names should be listed in all capitals below title, one author per line, with double-spacing between names. In footnotes on Page 1, please identify departmental source of article and staff and academic ranks of all authors.

Abstract. A suitable summary, or abstract, should be prepared for each manuscript. This will precede the article. The abstract should contain all the conclusions of the article itself.

Figures should be drafted in black India Ink, with legends typed on a separate sheet in numerical order, using Arabic numbers corresponding to figures. Glossy photographs are preferred to original charts. Medical drawings may be submitted in the original or glossy prints. Photographs and Figures should be lightly identified on back, as to number and "Top," together with last name of author. Use Roman numerals to designate Tables, and include descriptive headings under numbers. Indicate in text where Figures and Tables occur.

Abbreviations preferred are: ml, kg, gm, mg, μg, mm, and mEq/1.

References. Number references serially in text, and list in numerical order, beginning on a new page, as follows:

1. Gary GW, Bryan AC, Frayser R, Houston CS, Rennie IDB: Control of acute mountain sickness. Aerospace Med 42:81, 1971

List book references as follows:

2. Rafelson ME Jr, Brinkley SB, Hayashi JA: *Basic Biochemistry. Third Edition.* New York, Macmillan Company, 1971, pp. 96-208

Abbreviations of journals should correspond to those in *Index Medicus.*

Reprints. One hundred reprints with identifying cover are supplied free of charge for each article published. Additional reprints are supplied at cost.

COMPARISON OF TUBULAR NEPHROSIS PRODUCED BY MERCURIC CHLORIDE WITH NEPHROSIS DUE TO N-BROMOACETYL ALPHA AMINO ACIDS

George Y. Hsu
George Kalin
G. Michael Hass

ABSTRACT. N-bromoacetyl-D-phenylalanine, an irreversible inhibitor of carboxypeptidase A, and similar derivatives of D-tryptophan and D-alanine, when given intraperitoneally to rats at a daily dose of 4 mg/100 g body weight, produced a severe nephrosis. A similar tubular disease was also produced by mercuric chloride at about one-twentieth molar dose. The substituted alpha amino acids were equally toxic to mouse embryo fibroblasts and rat renal epithelial cells in tissue culture with cells becoming non-viable at reagent concentrations of about twenty μg/ml. This lethal level compared favorably with that found in the urine of rats with nephrosis due to the substituted amino acids. When N-bromoacetyl-D-phenylalanine and mercuric chloride were given together, the nephrosis was no more severe than that caused by each reagent alone. The results indicated that this class of alkylating agents has a different site of action than mercury on renal tubular epithelium, that the action may be due to affinity labeling of intracellular enzymes concerned with amino acid transport, and that similar compounds of bacterial or other origin may have a causal role in idiopathic nephrosis in man.

From the Department of Pathology, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois, and the Department of Biochemistry, University of Washington, Seattle, Washington

This work was supported by USPHS Grant NS-04872, the Otho S. A. Sprague Memorial Institute, and the Albert M. Day Fund

George Y. Hsu, M.D., Resident in Pathology, Presbyterian-St. Luke's Hospital; Assistant in Pathology, Rush Medical College

George Kalin, B.S., Research Assistant in Pathology, Presbyterian-St. Luke's Hospital

G. Michael Hass, Ph.D., Research Assistant Professor of Biochemistry, University of Washington

It is known that N-bromoacetyl-D-phenylalanine irreversibly inactivates the pancreatic enzyme, carboxypeptidase A, *in vitro*. This is due to specific alkylation of a critical amino acid residue at the active site of the enzyme.[1]

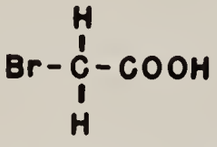
This experimental approach, termed affinity labeling, involves modification of a protein by a reagent possessing a chemically reactive group and structure which induce specific binding to the protein.[2-4]

Affinity labeling has been of great value in the study of mechanisms of ac-

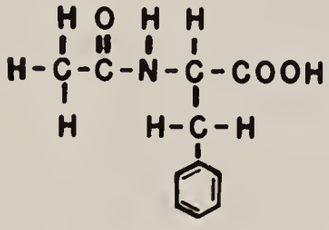
tion of several purified enzymes *in vitro* but not *in vivo*. This report is concerned with a continuing study, first reported last year, of the effects of the carboxypeptidase A inhibitor, bromoacetyl-D-phenylalanine and related compounds *in vivo*.

The structural formulas of N-bromoacetyl-D-phenylalanine and two derivatives used in the experiments are shown in Fig. 1.

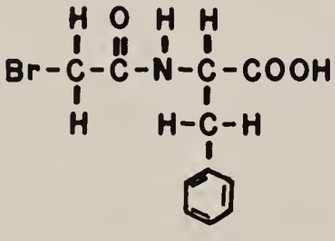
All reagents were prepared at fifty-six thousandth molar concentrations in buffered solutions, pH 7.4. They were given in appropriate amounts to young Sprague-Dawley rats by intraperitoneal, intramuscular or intracardiac routes. In each instance, control animals were given equimolar amounts of bromoacetate and N-acetyl-D-amino acids—the most likely



BROMOACETIC ACID



ACETYL-D-PHENYLALANINE



BROMOACETYL-D-PHENYLALANINE

Fig. 1—This represents the structural formulas of the nephrotoxic reagent, N-bromoacetyl-D-phenylalanine, and two likely metabolic derivatives which had no nephrotoxic action.

derivatives of the parent compounds. Bromoacetate has about the same alkylating reactivity and the N-acetyl-D-amino acids are the debrominated structural analogs of the parent compounds.

The minimal effective daily dose of N-bromoacetyl-D-phenylalanine was about 4 mg per 100 g body weight. This produced slight renal tubular necrosis, proteinuria and glycosuria within 24 hours (Fig. 2).

A more severe tubular necrosis occurred within 48 to 72 hours after injection of 8 mg N-bromoacetyl-D-phenylalanine per 100 g body weight (Fig. 3).

With continuation of the low dosage for three to four weeks, the pure renal tubular disease, not only increased in severity, but also displayed conspicuous regenerative changes with cystic dilatation of many tubules, as illustrated in Fig. 4. Characteristic protein casts containing curious basophilic droplets were always prominent. Despite the severe progressive nephrosis and tubular necrosis, there were no infiltrating inflammatory cells or glomerular lesions.

The first question to be answered was whether the nephrosis might be due to derivatives of the parent compound. Bromoacetate in equimolar amounts proved to be toxic to the animal but did not produce nephrosis. N-acetyl-D-phenylalanine was not harmful.

The next question was whether the observed nephrosis was a specific effect of one carboxypeptidase inhibitor. N-bromoacetyl-D-tryptophan and N-bromoacetyl-D-alanine were prepared and given intraperitoneally. Each produced the characteristic nephrosis when given in the same molar amounts as the inhibitor, N-bromoacetyl-D-phenylalanine.

This directed our attention to the use of other related compounds. Alpha methyl paratyrosine, a competitive inhibitor of catecholamine synthesis, has been reported to be a renal toxin.[5] In our studies it was tolerated in very large doses without harmful effects. Iodoacetamide had a toxic and lethal action similar to bromoacetate, but in each instance

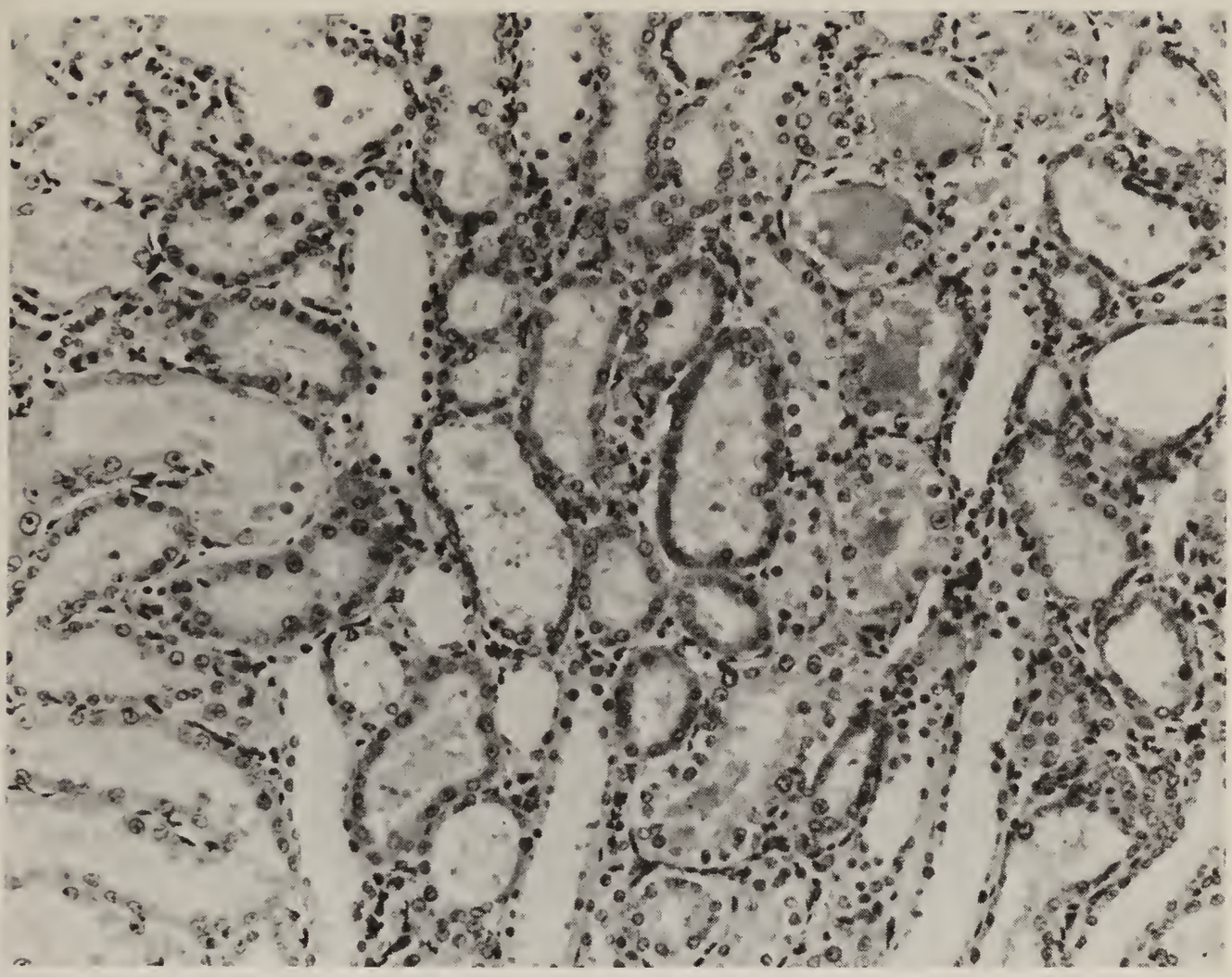


Fig. 2—This photomicrograph illustrates effect of a minimal nephrotoxic dose of N-bromoacetyl-D-phenylalanine and comparable compounds of tryptophan and alanine. This is apparent within two hours. Note the degeneration of epithelium of the convoluted tubules of the rat renal cortex. There is a modest amount of protein in the lumina of the tubules. There is no inflammatory cell reaction at this or any subsequent nephrotic stage.

there was no renal tubular disease. The same results were obtained with bromoacetyl-meta-benzoic acid. No nephrosis developed. At the moment, it seems that the induction of this type of nephrosis is restricted to alpha amino acids with bromoacetylated alpha amino groups.

The next question was whether these compounds might be toxic to cells grown in tissue culture. The N-bromoacetyl derivates of the three alpha amino acids, phenylalanine, tryptophan and alanine, proved to be lethal for rat adult kidney cells when used in concentrations of 20 to 40 μg/ml culture medium. Rat embryo fibroblasts were more resistant, although inhibition of cell multiplication occurred at the given reagent concentrations over a period of five days of cultivation.

Calculations based upon the concentration of radioactive products in the urine following injections of C^{14} labeled N-bromoacetyl-D-phenylalanine indicated that nephrosis was induced at about the same concentration of the reagent that killed adult rat kidney cells in tissue culture.

The nephrosis produced by these reagents had more than a superficial resemblance to nephrosis produced by mercury.[6-8] The degree of nephrosis produced in 15 to 22 days by daily intraperitoneal injection of 4 mg of N-bromoacetyl-D-phenylalanine per 100 g of body weight resembled that produced by daily intramuscular injections of one-tenth mg of mercury, as mercuric chloride, per 100 g of body weight, in 15 to 22 days. It was of interest that the use of

these two reagents in the same animal at the same time produced less nephrosis than each used alone. It was concluded that the two reagents do not reduce the viability of renal tubular epithelium by the same mechanism.

The data, thus far, indicate that the nephrosis is produced presumably by specific alkylation of renal tubular cell constituents by the N-bromoacetyl derivatives of three alpha amino acids given in the same molar amounts. These compounds are also toxic to adult rat kidney cells in tissue culture. The toxic effects in tissue culture become apparent at reagent concentrations similar to those in the urine of animals in which nephrosis is being induced. Inasmuch as other organs do not show cytopathic changes even when excessive amounts of the reagents are given, we suppose that the nephrosis is not simply the result of concentration of a generally cytopathic reagent but is probably due to interference by the reagent with some special renal tubular cell function involving amino acids.[9] Also, the nature of this interference is not the same as that due to mercury.

Our hypothesis is that there is a relation between the nephrotoxic action of these substituted amino acids and irreversible inhibition of intracellular carboxypeptidase-like enzymes or cathepsins.

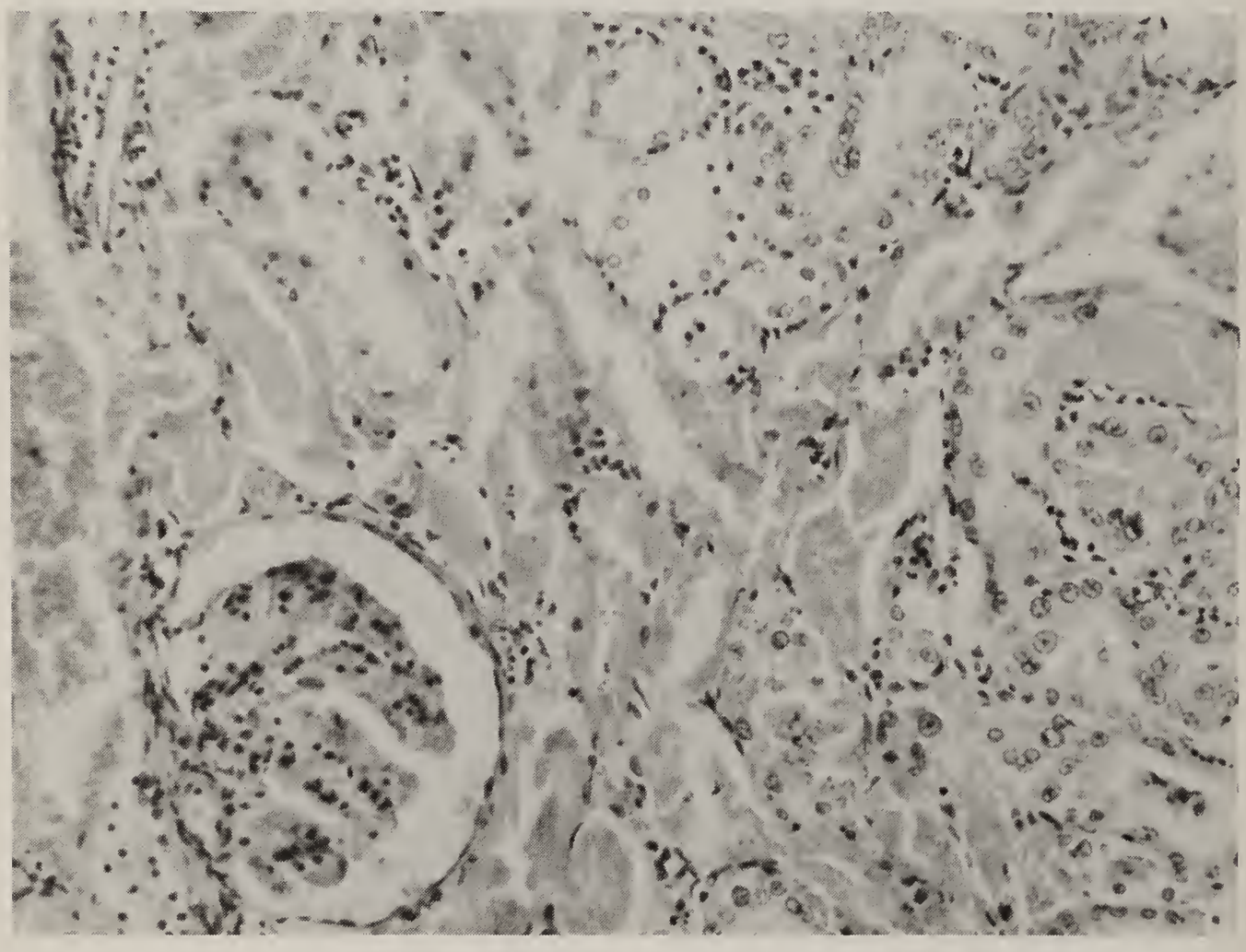


Fig. 3—This photomicrograph of the cortex of a rat kidney illustrates a near-maximal degeneration of convoluted tubular epithelium following use of the N-bromoacetyl compounds of alpha amino acids. Practically all convoluted tubular lining cells have undergone acute irreversible non-inflammatory degeneration and begun to separate from the basement membranes to accumulate in the lumina of tubules. At this stage, usually after 48-72 hours, anuria developed, if the daily dosage of the nephrotoxic reagents was as much as 8 mg/100 g of body weight.

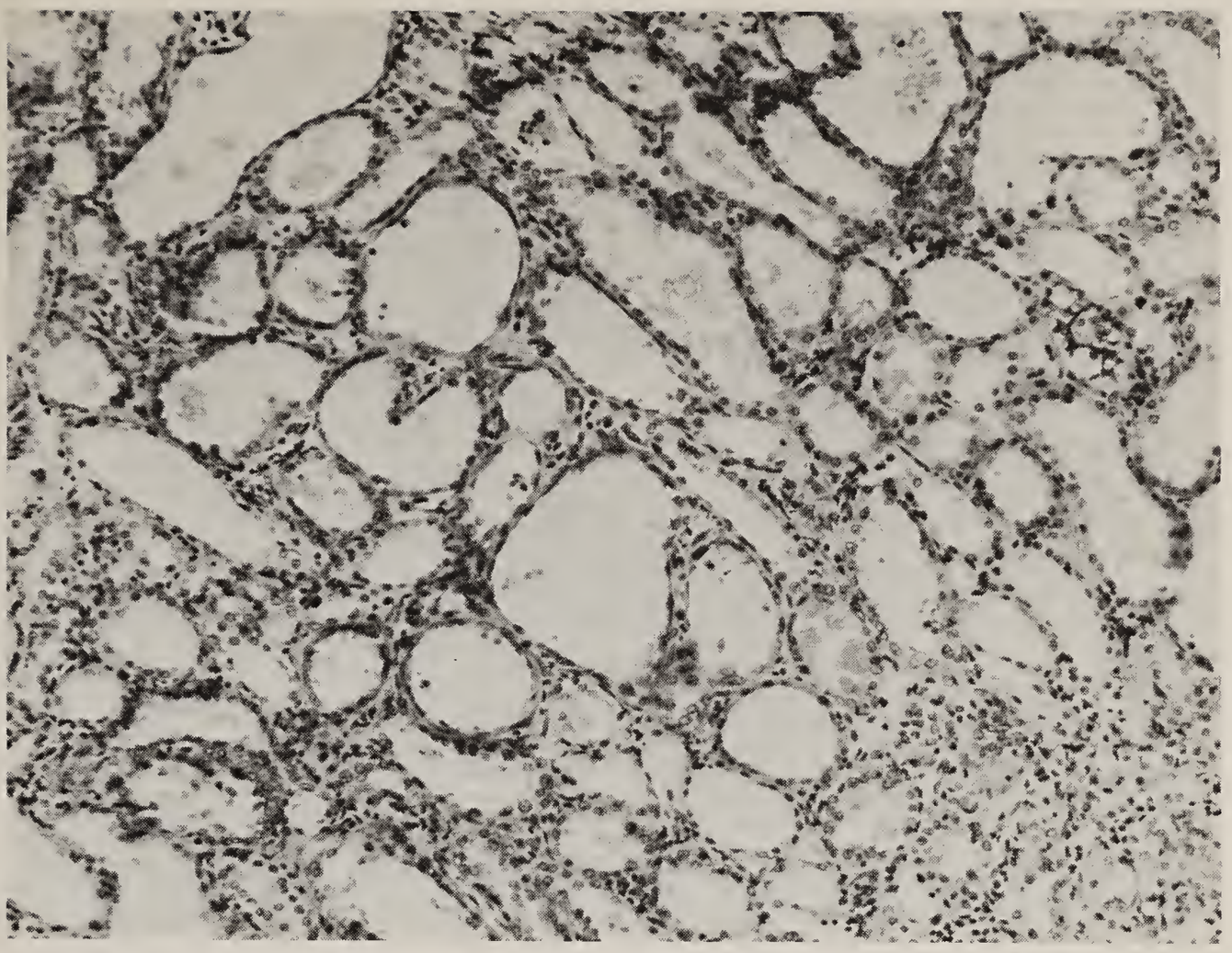


Fig. 4—This photomicrograph illustrates the usual appearance of the cortex of the rat kidney when the animal has received a low survivable dose of the nephrotoxic reagent each day for a period of fourteen to twenty-one days. Note that practically all normal epithelium of convoluted tubules has been replaced by flat, low-columnar, epithelial cells. This indicates total regeneration with little residual accumulation of protein and cellular debris in the lumina of tubules. This change is permanent.

This leads to the speculation that the action of similar compounds from bacterial or other sources might be nephrotoxic in man. Certainly, the pathogenesis of most cases of acute or chronic nephrosis in man is ordinarily obscure.

REFERENCES

1. Hass GM, Neurath H: Affinity labeling of bovine carboxypeptidase A by N-bromoacetyl-N-methyl-L-phenylalanine. I. Kinetics of inactivation. Biochemistry **10**:3535-3541, 1971. II. Sites of modification. Biochemistry **10**:3541-3546, 1971

2. Lipscomb WN, Hartsuck JA, Reeke GM Jr, Quiocho FA, Bethge PH, Ludwig ML, Steitz TA, Muirhead H, Coppola JC: The structure of carboxy-peptidase A. VII. The 2.0A resolution studies of the enzyme and of its complex with glycyltyrosine and mechanistic deductions. Brookhaven Symposia in Biology **21**:24-90, 1968

3. Hass GM, Neurath H: Protein Structure. In: Enciclopedia Italiana (in press, 1974)

4. Petra PH: Bovine procarboxypeptidase and carboxypeptidase A. Methods in Enzymology **19**:460-503, 1970

5. Moore KE, Wright PF, Bert JK: Toxicologic studies with alpha-methyl tyrosine, an inhibitor of tyrosine hydroxylase. J Pharm Exp Ther **155**:506-515, 1967

6. Oliver J, MacDowell M, Tracy A: The pathogenesis of acute renal failure associated with traumatic and toxic injury. Renal ischemia, nephrotoxic damage and the ischemic episode. J Clin Invest **30**:1307-1438, 1951

7. Rodin AE, Crowson CN: Mercury nephrotoxicity in the rat. Am J Path **41**:485-499, 1962

8. Flamenbaum W, McDonald FD, DiBona GF, Oken DE: Micropuncture study of renal tubular factors in low dose mercury poisoning. Nephron **8**:221-234, 1971

9. Meister A: On the enzymology of amino acid transport. Science **180**:33-39, 1973

REVIEW ARTICLE

THE USE OF VASOACTIVE DRUGS IN SHOCK

Richard M. Vazquez

ABSTRACT. Basic therapy of the shock state requires the restoration of adequate tissue perfusion. Also the various stages and types of perfusion defects require prompt specific correction. Vasoconstrictive reflexes, which may restore normal cuff blood pressures, are beneficial to the patient in shock, but only until the reflexes sacrifice local tissue nutrition to the extent that tissue necrosis becomes inevitable. Since the distribution of perfusion of tissue depends on many factors, each modifying agent may need to have its activity augmented or suppressed depending on the unique set of circulatory imbalances with which any patient presents.

Blood volume control represents a problem; the calculated normal blood volume for a given patient is correct only with a normally functioning cardiovascular system. When the cardiovascular system is profoundly altered, changes in blood volume make isovolemia a phenomenon relative to the functional status of the cardiovascular system. The pharmacologic augmentation of these physiologic mechanisms may be warranted, but also may need to be as varied as the mechanisms themselves. It is intended that the descriptions of the expected effects of the drugs discussed in this paper will aid in the selection and use of these vasoactive substances.

INTRODUCTION

The optimal management of patients in shock requires an understanding of the pathophysiologic mechanisms and the hemodynamic and biochemical events which take place during shock. Patients in shock have circulatory failure with inability adequately to perfuse vital organs with oxygenated blood. The following clinical signs together define shock: hypotension; weak, thready pulses; cool, pale, and clammy skin; tachycardia; peripheral cyanosis; oliguria; and mental confusion.[1] These findings may result from primary myocardial failure (pump failure), hypovolemia due to blood or fluid losses, anaphylaxis, or endocrine failure.

From the Department of Surgery, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois

Richard M. Vazquez, M.D., Resident in Surgery, Presbyterian-St. Luke's Hospital; Instructor in Surgery, Rush Medical College

HEMODYNAMIC EVENTS IN SHOCK

The cardiovascular system is similar to any other pump and conduit system in that its ability to maintain adequate organ perfusion depends on the output of the pump and the quality and distribution of the conduits. A decrease in "effective" cardiac output, which occurs early on in shock, may be due to primary pump failure, an absolute decrease in blood volume (hemorrhage), peripheral circulatory failure (relative hypovolemia followed later by absolute hypovolemia), or a combination of any of these. Arteriovenous shunting may, but need not accompany these states. In the presence of arteriovenous shunting the cardiac output may actually be increased, but the effective cardiac output, that is, the blood actually nourishing the tissues, may be reduced in volume by this circulatory short circuit.

Cardiac output is equal to the stroke volume multiplied by the heart rate per minute (Fig. 1). As is well known, the two are not independent. Tachycardia may decrease diastolic filling time to a point where ventricular filling is compromised, thereby causing a decreased stroke volume. The stroke volume is proportional to the ventricular filling pressure (Starling-Frank Law) and the myocardial contractility. The filling pressure may be affected by blood volume and ventricular compliance. Myocardial contractility is altered by the endogenous catecholamines, the quality of the myocardial muscle, and the blood supply to the myocardium.

At the bedside jugular venous pressure is a valuable guide to right ventricular filling pressure. Its limitations and the limitations of central venous pressure measurement as indicators of left ventricular filling pressure are self-evident.[1]

The relationship between blood flow, blood pressure, and the resistance of the vascular bed may be expressed as follows:

$$\text{FLOW} = \frac{\text{PRESSURE}}{\text{RESISTANCE}}$$

where flow equals the cardiac output, pressure is the arterial pressure, and the resistance is the calculated total peripheral resistance. Usually the blood pressure and cardiac output are measured and the resistance is calculated.*

The way that flow and resistance affect blood pressure can be seen in Fig. 2.

HEMORRHAGIC SHOCK

The most frequently used model for shock has been hemorrhagic shock in the dog. Lillehei, *et al.*[2] produced shock by bleeding the dogs to an arbitrary predetermined blood pressure (35 mm Hg) or by removing a predetermined percentage of the dog's blood volume. As the total blood volume is decreased, there is a decreased return of blood to the heart and a fall in the right atrial filling pressure. Cardiac output decreases and hypotension occurs.

The control of blood pressure is mediated by baroreceptors in the aortic arch and carotid sinus. Sympathoadrenal discharge from the hypothalamo-medullary axis is initiated by firing of the baroreceptors. Elevation of blood levels of catecholamines and other humoral factors occurs in an attempt to raise the blood pressure. Increase in sympathetic tone of the vascular musculature also occurs directly controlled by the central nervous system. Of all humoral factors liberated in acute hypotension, catecholamines are by far the most important.

During hypotension, blood flow is redistributed by local control mechanisms and the vasoconstrictive effect of the catecholamines. Since flow = pressure/resistance, an increase in local resistance

---

*Resistance (dynes-sec^{-1}/cm^5) =

$$\frac{\text{Press. gradient (mm Hg)} \times 1332 \text{ dynes/cm}^2}{\text{Blood Flow (cm}^3\text{/sec)}}$$

For systemic vascular resistance (SVR):

SVR =

$$\frac{\text{Mean aortic pres.} - \text{mean right atrial pres.} \times 80\dagger}{\text{Systemic Blood Flow}}$$

$$\dagger 80 \backsimeq \frac{1332 \text{ dynes/cm}^2 \times 60 \text{ sec}}{1000 \text{ cm}^3}$$

CARDIAC OUTPUT = HEART RATE X STROKE VOLUME

Fig. 1—Factors which affect stroke volume

STROKE VOLUME
- FILLING TIME
- FILLING PRESSURE
  - VENTRICULAR COMPLIANCE
  - BLOOD VOLUME
- MYOCARDIAL CONTRACTILITY
  - QUALITY OF MYOCARDIUM
  - MYOCARDIAL BLOOD SUPPLY
  - ENDOGENOUS CATECHOLAMINES

MECHANICAL ANALOG OF CARDIOVASCULAR SYSTEM

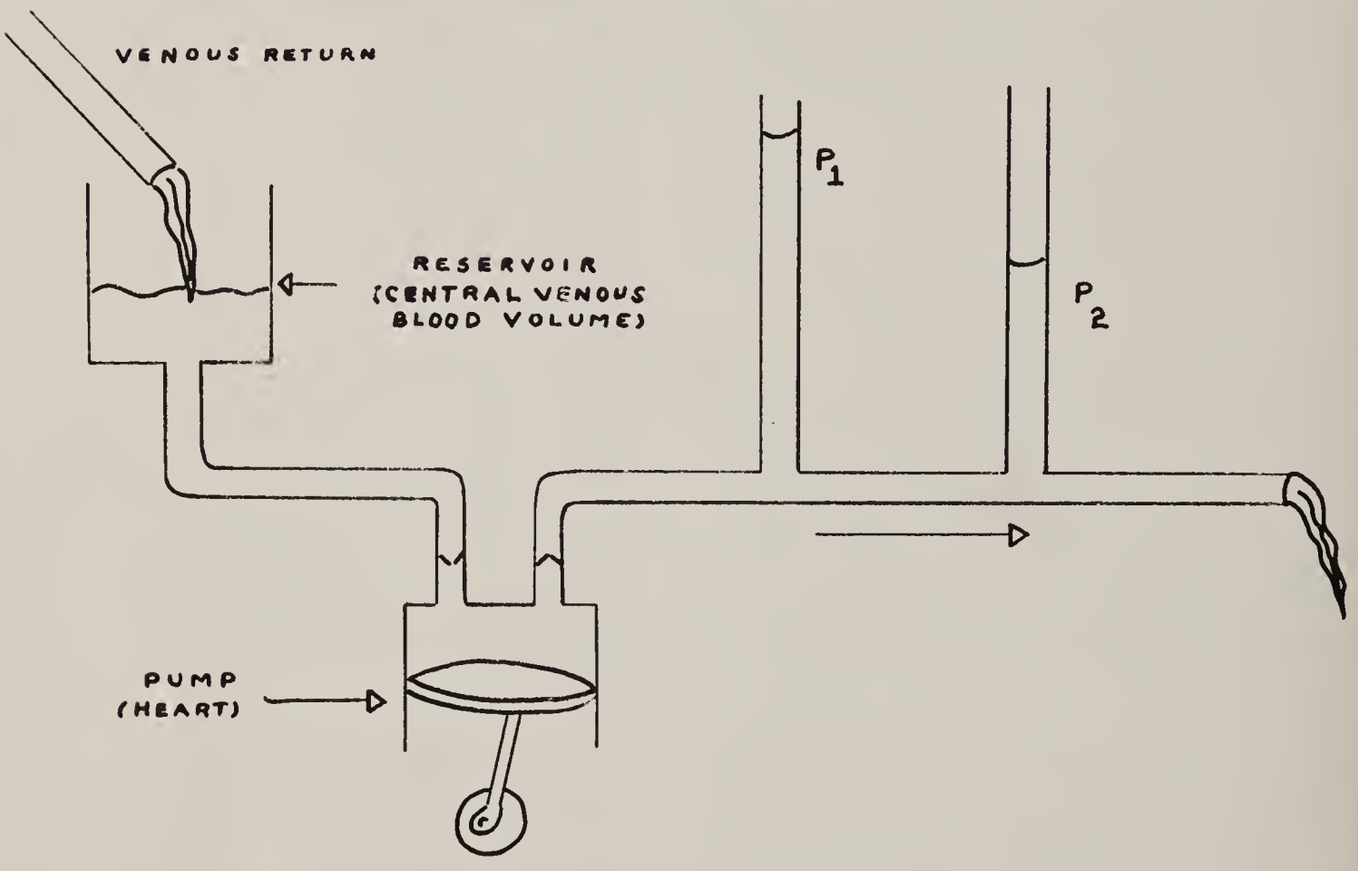


Fig. 2—Where P_1 and P_2 are pressures measured normal to the direction of flow, the pressure drop from P_1 to P_2 is determined by the rate of blood flow and the vascular resistance between P_1 and P_2. Flow is a measured parameter and the resistance is calculated. The resistance is inversely proportional to the 4th power of the radius. $\text{RESISTANCE} \propto \frac{\text{LENGTH X VISCOSITY}}{\text{RADIUS}^4}$

Rearranging the expression:

Pressure = Flow x Resistance

Let $P = P_1 - P_2$

$P_1 - P_2$ = Flow x Resistance

decreases local blood flow. But pressure = resistance × flow, so that this increase in resistance, while redistributing and decreasing local blood flow, helps to maintain the central arterial pressure.

In humans, the skin, skeletal muscles, splanchnic bed, and kidneys have a rich supply of sympathetic nerves, and the brain and heart do not. Thus, the former may have their blood supply markedly decreased by an excessive sympathetic response.

The terminology introduced by Ahlquist will be used in the further discussion of catecholamines and vascular response. Catecholamine receptors are designated alpha and beta.[3] Stimulation of the alpha receptors produces vasoconstriction while stimulation of the beta receptors produces peripheral vasodilatation. The cardiac receptors are all stimulatory and are beta receptors which enhance inotropic and chronotropic effect.

In addition to the vasoconstrictive attempts to normalize intravascular flow and pressure relationships, a compensatory shift of extracellular fluid into the vascular system also occurs early after blood volume decreases. When the capillary pressure falls below the average colloid osmotic pressure of 25 mm Hg, interstitial fluid moves into the vascular compartment.[4]

The precapillary and postcapillary arteriolar and venular sphincters have sensitive alpha receptors. An increase in their muscular tone from sympathetic discharge markedly reduces local blood flow to the point of ischemic anoxia. As compensatory mechanisms become overwhelmed, and if volume replacement is insufficient, an increase in anaerobic metabolism secondary to tissue anoxia allows the buildup of local tissue acid metabolites. The precapillary arteriolar sphincters function poorly at a low pH so that these sphincters relax while the postcapillary venular sphincters remain closed.[5]

The peripheral arterioles and venules have little elastin in their walls, which are mostly comprised of smooth muscle. Under vasomotor tone the small vessels manifest instability when the smooth muscle is contracted to the point that the elastic fibers are unstretched. In hypotension, the intraluminal pressure decreases, the unchanged vasomotor tone then acts against a lesser force, and the vessel radius decreases. If the tension exceeds a critical value or the pressure falls below a critical level, the vessel collapses. This is called the critical closure of the vessel.[4]

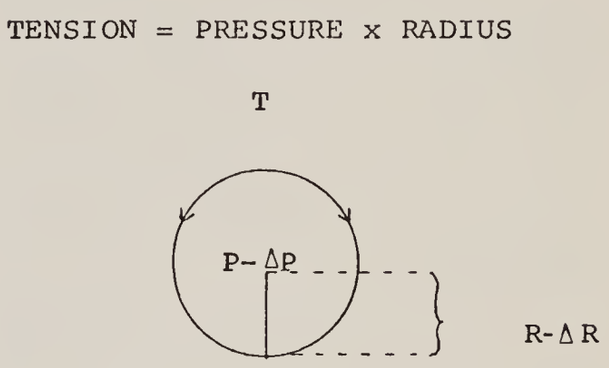


Fig. 3—As active tension exceeds (P — △P) (R — △R), critical closure occurs (after Burton[4])

If the wall tension is increased from its tonus level by catecholamines, the response may be to further decrease perfusion of already underperfused regions through this critical closure mechanism. For an excellent and more thorough discussion of vessel critical closure, see Burton.[4]

Increases in hydrostatic pressure gradients which result from the opening of arteriolar precapillary sphincters and the continued closure of venular postcapillary sphincters result in stagnant tissue anoxia and forces intravascular fluids into the extravascular space. Endothelial damage which occurs during stagnant blood flow compounds the fluid losses by permitting fluid egress into tissue spaces.[2]

With small to moderate loss of blood (500-1000 cc for the adult human) the sympathetic response causes a valuable redistribution of blood flow to the heart and brain and maintains an adequate

arterial pressure. As long as losses are not excessive, or replacement is adequate to prevent hypotension, the protective mechanisms aid the human or animal. The vasoconstrictor activity produced by reflex sympathetic discharge is usually quite adequate, but the degree of vasoconstriction usually can be accentuated by the addition of exogenous alpha stimulators.[2]

Lillehei et al.[2] found in dogs in hemorrhagic shock a 25- to 150-fold increase in circulating catecholamines. The addition of exogenous vasopressors for the maintenance of systemic pressure intensified vasoconstriction but did not improve survival. The vasoconstrictive response can be abolished by removing the sympathetic innervation to the involved organ or area under consideration prior to hemorrhage.[6]

Many of the conclusions made from observations of dogs in hemorrhagic shock are applicable to humans; however, the splanchnic vasculature in the dog is particularly susceptible to sympathoadrenal discharge. In humans the most susceptible vascular beds are in the kidney, lung and skin. During a hemorrhagic crisis, most humans will respond to blood volume expansion to normalize their cardiovascular systems. Those who do not respond frequently require pharmacologic intervention.

CARDIOGENIC SHOCK

Cardiogenic shock is the result of a direct myocardial insult which results in an inadequate cardiac output to meet the tissue demands for oxygenation and perfusion. The insult may be a myocardial infarction caused by coronary occlusion, severe congestive heart failure, surgical or blunt trauma to the heart, or some other cardiovascular insult, such as massive pulmonary embolus. The cardiogenic shock seen after open heart surgery is given the name of low output syndrome.[7]

As the cardiac output in each of these states decreases, hypotension ensues, and the compensatory mechanisms of sympathoadrenal discharge are initiated. The same set of peripheral vascular events that occur in hemorrhagic shock occur, so that maintenance of arterial pressure through the administration of vasopressors has no beneficial effect on perfusion.

ENDOTOXIN SHOCK

Endotoxin shock is a state of cardiovascular collapse produced by the effects of a lipoprotein-carbohydrate complex found in the somatic "o" antigen present in the cell wall of gram-negative organisms.[8] Endotoxin shock has been produced experimentally by the intravenous injection of endotoxin, most frequently using dogs as a model. Aside from the microcirculatory differences referred to earlier between dogs and humans there are other differences in the experimental and natural production of the shock state. These need to be explained in some other way than on the basis of circulatory differences. Damage to other structures in the naturally occurring form of endotoxin shock presumably is the result of liberated proteolytic enzymes from the interior of gram-negative organisms during their destruction.

Endotoxin injected into the dog results in an immediate decrease in systemic blood pressure accompanied by a rise in portal vein pressure. Simultaneously, there is an increase in the histamine concentration of the hepatic vein blood and a marked constriction of the portal veins. Later, after a period of partial recovery, the blood pressure again falls, cardiac output decreases, catecholamine activity increases, peripheral blood flow and plasma volume are decreased and eventually death follows. Autopsy findings are similar to those in dogs who die in hemorrhagic shock. The major organ involvement is that of the mucosa of the small bowel, which in the dog is the site of intense sympathetic activity. Various other animals, including the human, manifest hemorrhagic infarction of the kidney and lungs. It seems that endotoxin activity is mediated through the formation of a proteolytic substance which causes the release of

histamine,[9] catecholamine,[9-11] serotonin,[12] acetylcholine,[13] and bradykinins,[13,14] all of which are potent vasoactive substances. Evidence has also been presented that endotoxin sensitizes and accentuates the vasoconstrictive response to epinephrine.[11]

The peripheral pooling secondary to endotoxin injection results in a decreased circulating blood volume (relative hypovolemia) and decreased cardiac output. The hypotension that ensues initiates sympathoadrenal responses which further increase the peripheral pooling already present. Precapillary arteriolar, but not postcapillary venular constriction ceases as acidosis occurs.

Blood volume loss occurs as hydrostatic pressures in the capillary bed increase, just as in hemorrhagic shock. In each of the forms of shock discussed, acidosis increases the coagulability of the blood, while, at the same time, stagnation encourages intravascular thrombosis. These processes may cause microcirculatory thrombosis, again compromising peripheral tissue perfusion. In endotoxin shock the endotoxin may directly initiate blood coagulation by activation of the Hageman factor, resulting in an even more favorable condition for the development of microcirculatory and peripheral thrombosis. It is commonly believed that endotoxin does not have a direct myocardial depressant effect, but this point is debatable.

A small number of patients with endotoxin shock have a high cardiac output which presumably occurs as the result of pulmonary or hepatic shunting of blood. These patients also manifest viscerocutaneous vasoconstriction and need to be treated in the same way as those with a low cardiac output and shock.

SIMILARITIES OF VARIOUS KINDS OF SHOCK

All of the types of shock discussed have certain features in common (Fig. 4). There is present in all forms an abnormal cardiac output, decreased perfusion, and intense peripheral vasoconstriction. The sympathetic nervous system overreacts in the same way in each form of shock. Various forms of therapy, all of which include careful monitoring of cardiovascular parameters, have been advanced. The major controversy among the proponents of the various therapeutic regimens has been over whether vasoconstricting or vasodilating agents should be used.

Early in the 1900's, it was recognized that intense vasoconstriction occurred in shock. In the late 1950's, independent work by Nickerson and Lillehei emphasized the importance of the use of vasodilating drugs in the management of shock. Studies directed toward an investigation of shock therapy have concerned themselves with hemodynamic data and recording morbidity and mortality of patients treated with many types of vasoactive substances, and their results have been responsible for the rationale of the use of vasodilating substances in shock (See Table).

Brown et al.[15] investigated the hemodynamic responses observable in clinical shock with the use of four sympathomimetic amines; norepinephrine, metaraminol, isoproterenol, and methoxamine. Norepinephrine, metaraminol, and methoxamine all increased systemic arterial pressure, central venous pressure, peripheral resistance, central blood volume, stroke work, and cardiac work. Norepinephrine caused a small increase in stroke volume. Isoproterenol increased all the above except that peripheral resistance was essentially unchanged. Cardiac output was increased from a mean output of 5.3 to 8.1 L/min. Since isoproterenol used alone only minimally decreases peripheral resistance, drug-induced increase in cardiac output alone cannot be utilized for peripheral perfusion. An increase in cardiac work should be associated with an increased cardiac output as it was with isoproterenol. When increased cardiac work occurs with an increase in peripheral resistance out of proportion to the increase in cardiac output, the efficiency of the heart is reduced.

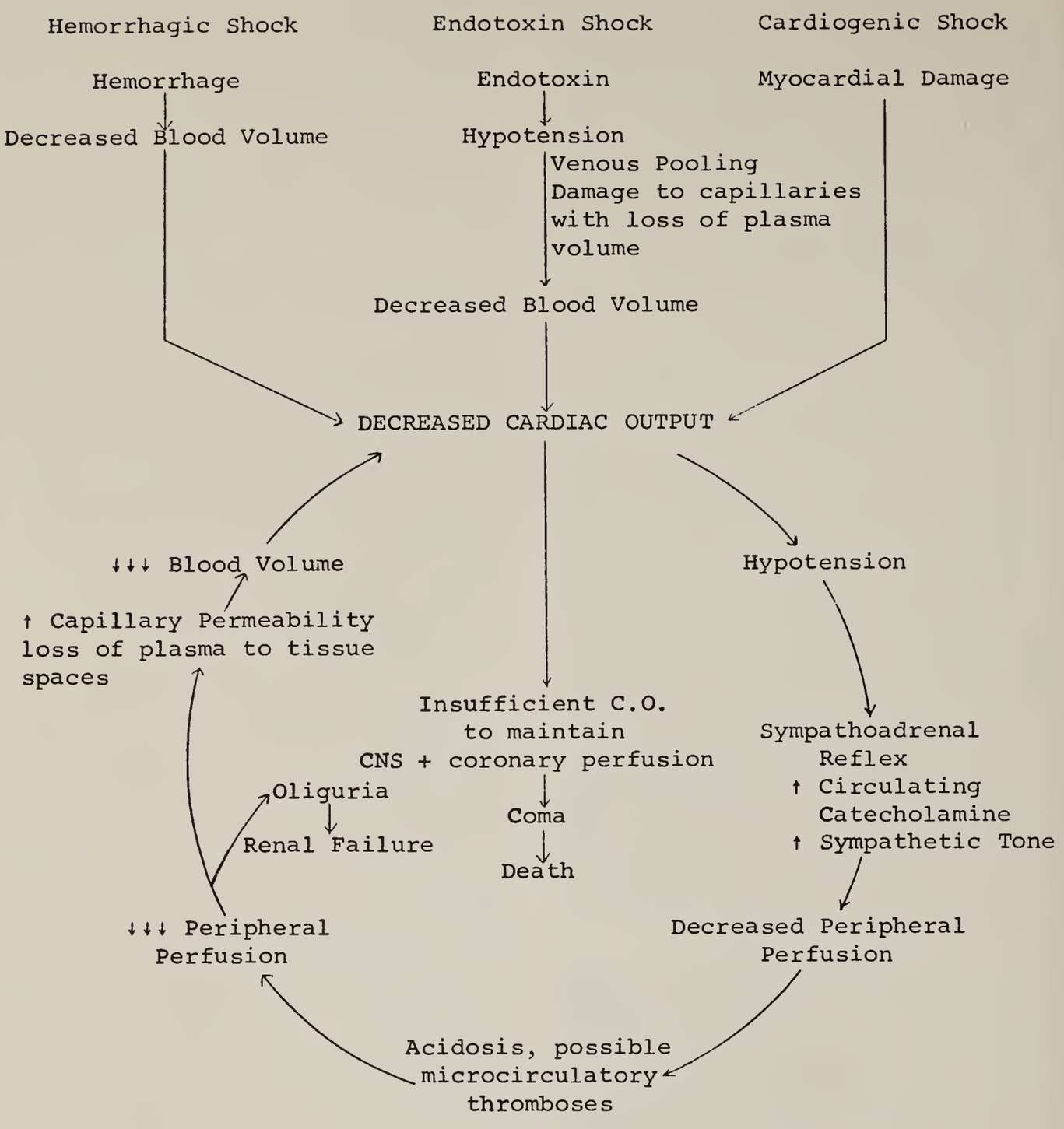


Fig. 4—Common factors in three major types of shock

Sympathomimetics

In most cases of shock, viscerocutaneous vasoconstriction is the rule, even though total peripheral resistance is decreased. A plausible explanation for this decrease is the opening of A-V shunts. As is evident, the vascular response is dependent on an intact sympathetic nervous system and a vascular system, capable of responding to catecholamines. Hypotensive states occuring with the use of halothane and methoxyflurane, high spinal anesthesia, extensive sympathectomy, severe anaphylaxsis, and sudden cardiac arrest, require the use of vasoconstrictors.[16] These states are associated with a "paralysis" of the sympathetic nervous system to such an extent that it may be totally unresponsive to hypotensive stimuli.

Numerous authors have found that

vasoconstrictive substances potentiate circulatory or cardiac failure. Exogenously administered norepinephrine and other alpha-stimulating agents have the same deleterious effects on the microcirculation as do endogenous catecholamines. Critical vessel closure occurs more easily, leading to peripheral vascular instability and further increases in total peripheral resistance.[4]

MacCannell et al.[17] investigated the use of dopamine, a precursor of norepinephrine, in hypotension and shock. The drug increases myocardial contractility and increases splanchnic and renal blood flow without causing peripheral vasoconstriction. The myocardial effects are a result of beta adrenergic activity, but its vascular effects cannot be blocked by alpha or beta adrenergic blocking agents. High doses of dopamine may cause a peripheral vasoconstriction not seen with the usual dose necessary for shock therapy, and this effect can be blocked by alpha adrenergic blockade. The toxic effects of the drug include nausea and vomiting which occur inconsistently even with prolonged administration.

Alpha Blocking Agents

By 1950, investigational trends had firmly proceeded toward a thorough investigation of the use of alpha adrenergic blocking agents, such as phenoxybenzamine. Before entering into a discussion of the use of alpha adrenergic blocking and other peripheral vasodilators, it should be emphasized that no drug of this type should be administered to a patient unless adequate volume replacement precedes and accompanies its use. Central venous pressure and other vital signs need continuous attention because of the profound vascular effect of these drugs.

Nickerson and Carter investigated the use of phenoxybenzamine as a protective agent in traumatic shock. They found that inhibition of vasoconstrictive responses by phenoxybenzamine given prophylactically provided effective protection against shock but increased susceptibility to the immediate deleterious effects of blunt trauma. The investigation utilized rats traumatized in a Noble-Collib drum as a shock preparation. The drug completely eliminated all late shock

TABLE

VASOACTIVE SUBSTANCES USED IN SHOCK

The following vasoactive drugs will be discussed:		
Generic Name	**Trade Name**	**Action**
Methoxamine Hydrochloride	Vasoxyl®	Pure alpha stimulator
Norepinephrine	Levophed®	Both have alpha stimulating effects peripherally and beta cardio-stimulatory effects.
Metaraminol Bitartrate	Aramine®	
Dopamine Hydrochloride		Beta cardiac effect Unknown peripheral dilator effect
Isoproterenol	Isuprel®	Pure beta cardiac and peripheral vasodilatation
Phenoxybenzamine	Dibenzylene®	Pure alpha blocking agent
Chlorpromazine	Thorazine®	Peripheral vasodilator
Hydrocortisone	Solu-Cortef®	Peripheral vasodilator
Methylprednisolone	Solu-Medrol®	Peripheral vasodilator
Phentolamine	Regitine®	Peripheral vasodilator

deaths and increased overall survival. The drug did appear to cause an increase in intraperitoneal hemorrhage due to traumatic rupture of the liver or spleen.[18]

The clinical use of phenoxybenzamine in septic shock was investigated by Skoldborg in 1968.[19] Twenty-six such patients were given the drug at intravenous infusion rates of 1 to 2 mg per kg of body weight over one hour. As emphasized in other series, the infusion was supplemented by volume administration. Eighteen of the 26 patients recovered from their shock. Within 24 hours of the initiation of phenoxybenzamine therapy, most of the patients were stable enough for surgical therapy of the cause of their sepsis when such a cause was discovered.

Phenoxybenzamine is thought to inactivate alpha receptor sites so that they are no longer responsive to alpha stimulating agents. Phenoxybenzamine does not affect the action of epinephrine or norepinephrine upon the intestinal smooth muscle nor upon the myocardium. The latter point is the basis for adding phenoxybenzamine during the use of these agents so that only their cardiac effects are realizable. The effect of the drug starts slowly, about one hour after intravenous injection, and lasts two to four days. Fifty per cent is eliminated through the kidneys in 12 hours and the rest within one week.

Occasionally, sudden mobilization of pooled blood in response to phenoxybenzamine, especially in the presence of myocardial failure, results in acute pulmonary vascular overload. Phlebotomy is indicated in this event.

Shortly after the initiation of phenoxybenzamine therapy the systolic and diastolic blood pressures decrease. Within five to ten minutes cutaneous vasodilatation becomes evident. The CVP begins to rise in 15 to 20 minutes. Frequently the diastolic pressure rises before the systolic. Some patients in Skoldborg's series appeared to have normalized both their blood pressure and capillary function within one hour of administration. Occasionally relapses occurred and one or two further doses of phenoxybenzamine were required. For an excellent discussion of the clinical use of this drug see Skoldborg.[19]

Lillehei et al. performed much of the investigational work presented in this paper on the pathophysiology of hemorrhagic shock. They reviewed the action of many of the drugs discussed. They found that agents which caused vasoconstriction either directly (norepinephrine) or indirectly (iproniazid), when combined with usually sublethal doses of endotoxin, exhibited a synergistic effect in the production of irreversible shock. An increase of mortality from 0 to 100% occurred with the vasoconstrictor-endotoxin combination. Hypothermia, heparin, intestinal antibiotics, or exchange transfusions had no evident effect on shock. The only drugs which changed survival in shock were phenoxybenzamine, hydrocortisone, and chlorpromazine.

Corticosteroids

The effects of pretreatment of dogs with large doses of hydrocortisone (15 to 25 mg per kg body weight intravenously) had the same protective effect on dogs in endotoxin shock as did phenoxybenzamine pretreatment. Unfortunately most of us do not know ahead of time when a patient will develop endotoxic shock, so Lillehei's group investigated the treatment of pre-existing endotoxic shock with hydrocortisone. They showed that a gradual decrease in total peripheral resistance occurred, and cardiac output slowly began to rise. The worsening of hypotension seen with other more potent vasodilators, without coincident volume replacement, is not seen with hydrocortisone used alone (50 mg per kg intravenously).[20] Further investigations demonstrated that methylprednisolone gave results similar to those obtained with hydrocortisone. Lillehei observed a 50 percent survival rate in dogs treated with the above dose of hydrocortisone as opposed to a 100 percent mortality rate in those untreated. Steroids combined with volume replacement yield an 80 percent survival rate, a

rate observed for dogs in similar groups treated with phenoxybenzamine and volume replacement.

The cardiovascular effects of pharmacologic doses of steroids have been difficult to establish because of their variability. Wilson and Fischer[21] found that cardiac output and peripheral resistance began to normalize one hour after the injection of steroids (50 mg per kg body weight intravenously over five minutes) regardless of the aberrations seen during shock. The study was done utilizing 22 patients in shock. High cardiac outputs decreased toward normal as their concomitant low peripheral resistances normalized. Low cardiac outputs and high peripheral resistances underwent opposite but normalizing changes. Sambhi et al. noted similar findings.[22]

Sullivan and Cavanaugh[23] found that a selective renal vasodilatation occurred in dogs in shock as a result of the administration of steroids.

The doses of steroids are critical when they are used in the human adult to obtain the hemodynamic results desirable in shock. A small dose, 150 to 300 mg, in humans, will augment the vasoconstrictive effects of catecholamines while doses equivalent to 2,000 to 6,000 mgm of hydrocortisone given intravenously every 24 hours elicit the desired effect. Short-term administration of these large doses does not require tapering of steroids for withdrawal. A history of peptic ulcer disease does not contraindicate their use in hemorrhagic shock.[5]

Other Alpha Blocking Agents

The benefits of peripheral vasodilatation during shock have been elucidated by the above studies. Other agents which have been used to this effect are phentolamine (Regitine®) and chlorpromazine. Regitine is a short-acting competitive inhibitor of alpha adrenergic receptor sites.[5] Its effects can be reversed rapidly with norepinephrine.

Kilman[24] found that chlorpromazine, when given to dogs undergoing cardiopulmonary bypass, tended to cause a decrease in total peripheral resistance and improve peripheral perfusion. Cardiac output was controlled by the pump.

Dietzman et al.[7] have used chlorpromazine in the treatment of post-cardiac surgery low-output syndrome in adult humans with a dose of five mg intravenously initially and repetition of the dose until the desired effect is achieved or CNS depression occurs. Improvement was noted in patients for whom therapy was begun before 8 to 10 hours of low cardiac output had elapsed.

Gokhale et al.[25] investigated the cardiovascular mechanisms of action of chlorpromazine and found that it acted not only as an alpha blocking agent but also as a potentiator of beta adrenergic vasodilatation.

Loeb et al., in a study which involved 13 patients in shock, used total doses of 15 to 20 mgm of chlorpromazine intravenously. All patients responded with a fall in mean blood pressure, cardiac output increase by an average of 20 percent and systemic vascular resistance decrease by an average of 29 percent.[26]

Prostaglandins

A class of drugs which has not yet been investigated for use in shock is the prostaglandins, especially PGE_1 and PGA_1. These drugs are potent depressors and stimulators of smooth muscle found in the seminal vesicles of sheep and humans. The cardiovascular effects of PGA_1 and PGE_1 given intravenously are a decrease in atrial pressures, an increase in heart rate, pulmonary artery pressure, cardiac output, and myocontractile force. However, both are vasodilators and decrease both systemic arterial pressure and total peripheral resistance. The myocardial effects appear to be direct and are not blocked by propranalol (Inderal®).

These responses are those which are sought when combinations of vasodilators and inotropic drugs are used.

DISCUSSION

The data which have been presented are the basis of modern trends in shock therapy. Volume management is an ab-

solute necessity. Cardiorespiratory failure must be guarded against, and treatment of the etiology of the shock state must be initiated early. Pharmacologic intervention may be necessary, but the choice of agents must be closely governed by the clinician's proper assessment of the cardiovascular system. The microcirculation as well as the myocardium must be treated when indicated.

Treatment of the microcirculation begins with proper volume restoration. Deleterious peripheral vasoconstriction may then be carefully inhibited. The choice of which of the vasodilators to use depends on several considerations, not the least of which is drug availability.

Phenoxybenzamine is available for investigational purposes only, but may be the drug of choice because of its lack of extravascular effects and the fine results obtained with its cautious use. Phentolamine, because it is so short acting, needs to be given as a continuous intravenous preparation. Phentolamine exerts in general the same peripheral vascular effects as does phenoxybenzamine. The onset of its action occurs several minutes after intravenous injection, rapidly maximizes and disappears several minutes after the infusion is discontinued. The advantages of using this drug instead of phenoxybenzamine are related to this short duration of action. When, in spite of seemingly adequate volume replacement, the administration of a vasodilator unmasks hypovolemia, phentolamine infusion can be interrupted for further volume replacement. A disadvantage of isoproterenol is that it may cause a rather severe tachycardia. Also, it must be given continuously and has less than an optimal effect on the microcirculation. Adrenocortical steroids, while usually available, are expensive and may not be of much use in the all-too-frequent problem of shock occurring in a patient already on moderate doses of steroids; for example, a postoperative, steroid-dependent patient with a collagen disease. However, because the cardiovascular effects of pharmacologic doses of steroids are not as profound as those of alpha blocking agents, the steroids may be used more safely in a clinical situation where complete monitoring of the patient's cardiovascular parameters cannot be accomplished. Their use in the occasional patient with a "steroid" ulcer as the etiology of shock is questionable. Chlorpromazine, while inexpensive and usually available, may, because of its CNS depressive effects, complicate neurological evaluation and predispose to atelectasis, aspiration, etc. All of these factors need be considered when one initiates vasodilator therapy.

AN OUTLINE FOR THE CLINICAL MANAGEMENT OF SHOCK

On a surgical service one will likely see a number of patients who have been undertransfused. Volume replacement may be all that is necessary in these patients to correct hypotension. Those who do not respond favorably and quickly to volume replacement need more intricate management.

The possibility of an intraoperative or postoperative myocardial infarction must be considered and an electrocardiogram obtained. Careful fluid management requires a central venous catheter and a catheter in the urinary bladder. Blood cultures should be drawn early when sepsis is a possible etiology. Institution of appropriate parenteral antibiotic therapy should follow the obtaining of cultures from the respiratory system, bladder, blood, drainage sites, etc. These measures, which take only minutes, are of inestimable aid later on in the management of the patient.[28]

The importance of the CVP does not necessarily lie in its initial value. The normal range in a supine patient is −3 cm H_2O to +12 cm H_2O. What is important is the direction and rate of change of the CVP. Frequent physical examination of the patient and gathering of clinical history, if possible, is necessary for the care of these patients. If hemorrhage is the etiology of shock, then swift local control, when possible, is indicated.

As a test for hypovolemia, 500 cc of 5 percent human serum albumin may be given intravenously over a one-hour period. The vital signs and CVP should be closely watched. A deterioration of the patient and a rising CVP $\geq$ 15 cm H_2O indicate circulatory overload and/or pump failure.

If a peripheral vasodilator is indicated, 2 gm of methylprednisolone (Solu-Medrol®) intravenously over five minutes and repeated every eight hours may be itniiated. This form of therapy may be discontinued in 48 to 72 hours without tapering the dose. Chlorpromazine, 2.5 mg to 5 mg intravenously as an initial dose, may be given and repeated as necessary. It may be used alone or in combination with a drug such as isoproterenol.

Particular attention must be paid to renal function, pulmonary insufficiency (shock lung) and the coagulation mechanism.

Pulmonary damage caused by nonthoracic trauma or shock is manifested by pathologic change of vascular congestion, perivascular hemorrhage, peribronchial hemorrhage, protein-containing pulmonary edema and intra-alveolar hemorrhage.[29] As a result of pulmonary microvascular transmural pressure relationships which exist during shock, fluid leaks into the interstitial spaces in the lung. Surfactant production decreases as the pulmonary parenchyma is damaged. The combination of these events produces an oxygen diffusion barrier as well as a ventilation-perfusion alteration. These two mechanisms are responsible for the arterial hypoxemia which produces the clinical picture termed shock lung. Shock lung has been referred to as "the wet lung syndrome," "congestive atelectasis," "post-pump lung," "post-traumatic pulmonary insufficiency," and several other synonymous terms. Tachypnea, cyanosis and restlessness out of proportion to what might be expected from physical examination and chest x-ray may be the first signs of shock lung.

Pulmonary microvascular damage may then occur as a result of sequestration of segmented polymorphonuclear cells which liberate their cytotoxic enzymes. This damage may be compounded by local platelet aggregations and the liberation of vasoconstrictive substances by these trapped platelets.

The aims of therapy are restoration of adequate pulmonary perfusion by ventilatory management, and the early use of corticosteroids to prevent cellular pulmonary damage.

Another reason for the early initiation of steroid therapy in shock is the beneficial effect of these pharmacologic doses on the lung.

The steroid which has been most extensively studied and successfully utilized in the treatment of shock lung is methylprednisolone sodium succinate (Solu-Medrol®, Upjohn).[30] The beneficial effects of this drug in pharmacologic doses in the prevention of shock lung are reason enough to give the drug even if an additional vasodilator is utilized. The complete therapy of this complication is out of the scope of this discussion, but must be swift and correct to save the life of the patient.

Intravascular sequestration of segmented polymorphonuclear cells with liberation of their cytotoxic enzymes results in pulmonary microvascular damage.

Acid-base derangements should be managed as they arise.

APPENDIX

The doses of drugs mentioned in this paper which have not been explicitly stated are the following:

a. Norepinephrine 8 mg/L
b. Metaraminol bitartrate 200 mg/L
c. Methoxamine sulfate 200 mg/L
d. Isoproterenol 2 mg/L
e. Dopamine 1% solution
f. Phentolamine (suggested solution) 50 mg/500 cc (individual patient's response require titration; administration with Harvard® infusion pump is helpful)

The solutions were administered at the following rates:

a. 0.35-0.53 μg/kg/min
b. 9-13 μg/kg/min
c. 0.02-0.15 μg/kg/min
d. 9-13 μg/kg/min
e. 0.5-10.0 μg/kg/min
f. 0.5-1.0 mg IV/min

References

1. Abboud FM: The sympathetic nervous system and alpha adrenergic blocking agents in shock. Med Clin N Amer **52**:1049, 1968
2. Lillehei RC, Longerbeam JK, Bloch JH, Manax WG: The modern treatment of shock based on physiologic principles. Clin Pharmacol Ther **5**:63, 1964
3. Ahlquist RP: A study of the adrenotropic receptors. Amer J Physiol **153**:586, 1948
4. Burton AC: *The Physiology and Biophysics of the Circulation*. Chicago, Year Book Medical Publishers, Inc., 1966, p 80
5. Christy JH: Treatment of gram-negative shock. Amer J Med **50**:77, 1971
6. Fine J: *The Bacterial Factor in Traumatic Shock*. Springfield, Illinois, Charles C. Thomas, Pub., 1954
7. Dietzman RH, Ersek RA, Lillehei CW, Castaneda AR, Lillehei RC: Low output syndrome: Recognition and treatment. J Thorac Cardiovasc Surg **57**:138, 1969
8. Christy JH: Pathophysiology of gram-negative shock. Amer Heart J **81**:694, 1971
9. Spink WW: Endotoxin shock. Ann Intern Med **57**:538, 1962
10. Lillehei RC, Longerbeam JK, Bloch JH, Manax WG: Nature of irreversible shock: Experimental and clinical observations. Ann Surg **166**: 682, 1964
11. Zweifach BW, Nagler AL, Thomas L: The role of epinephrine in the reactions produced by endotoxins of gram-negative bacteria. II. The changes produced by endotoxin in the vascular reactivity to epinephrine in the rat mesoappendix and isolated perfused rabbit ear. J Exper Med **104**:881, 1956
12. Davis RB, Meeker WR: Serotonin release by bacterial endotoxin. Proc Soc Exper Biol Med **108**:774, 1961
13. Thal AP, Wilson RF: Shock, in *Current Problems in Surgery*. Chicago, Year Book Medical Publishers, Inc., 1965
14. Thal AP, Sardesai VM: Shock and the circulating polypeptides. Amer J Surg **110**:308, 1965
15. Brown RS, Carey JS, Mohr PA, Monson DO, Shoemaker WC: Comparative evaluation of sympathomimetic amines in clinical shock. Circulation **34**:260, 1966
16. Baue AE: Recent developments in the study and treatment of shock. Surg Gynec Obstet **127**:849, 1968
17. MacCannell KL, McNay JL, Meyer MB, Goldberg LI: Dopamine in the treatment of hypotension and shock. New Eng J Med **275**:1389, 1966
18. Nickerson M, Carter SA: Protection against acute trauma and traumatic shock by vasodilators. Canad J Biochem **37**:1161, 1959
19. Skjoldborg H: Phenoxybenzamine in the treatment of septic shock. Acta Chir Scand **134**:85, 1968
20. Motsay GJ, Dietzman RH, Ersek RA, Lillehei RC: Hemodynamic alterations and results of treatment in patients with gram-negative septic shock. Surgery **67**:577, 1970
21. Wilson RF, Fisher RR: The hemodynamic effects of massive steroids in clinical shock. Surg Gynec Obstet **127**:769, 1968
22. Sambhi MP, Weil MH, Udhoji VN: Acute pharmacodynamic effects of glucocorticoids: Cardiac output and related hemodynamic changes in normal subjects and patients in shock. Circulation **31**:523, 1965
23. Sullivan TJ III, Cavanagh D: Corticosteroids in endotoxin shock: Effect on renal vasomotion. Arch Surg **92**:732, 1966
24. Kilman JW: Effect of chlorpromazine on peripheral blood flow. Surgery **66**:886, 1969
25. Gokhale SD, Gulati OD, Parker HM: An investigation of the adrenergic blocking action of chlorpromazine. Brit J Pharmocal **23**:508, 1964
26. Loeb H, Pietras R, Ninos N, Tobin J Jr, Gunnar R: Vasodilator effects of intravenous chlorpromazine in clinical shock. Circulation **38**:130 (Supp 6), 1968
27. Nakano J, McCurdy JR: Hemodynamic effects of prostaglandins E_1, A_1 and F_{2a} in dogs. Proc Soc Exper Biol Med **128**:39, 1968
28. Weil MH, Shubin H, Biddle M: Shock caused by gram-negative micro-organisms: Analysis of 169 cases. Ann Intern Med **60**:384, 1964
29. Wilson JW: Treatment or prevention of pulmonary cellular damage with pharmacologic doses of corticosteroid. Surg Gynec Obstet **134**:675, 1972
30. Unpublished data

PEDUNCULATED UTERINE LEIOMYOMA WITH PARASITIC BLOOD SUPPLY FROM THE SUPERIOR AND INFERIOR MESENTERIC ARTERIES

David J. Kurti
Suresh K. Patel
Jerry P. Petasnick

ABSTRACT. A case of benign pedunculated leiomyoma of the uterus with parasitic blood supply from the superior and inferior mesenteric arteries was studied arteriographically. Parasitic blood supply is an unusual finding and is usually associated with malignant invasion of neighboring structures, although, as in this case, it may be seen in benign hypervascular tumors.

INTRODUCTION

Angiography can provide valuable information in the diagnostic evaluation of mass lesions of the female pelvis. For example, the arteriographic appearance of the uterine arteries has been shown to be reliably useful in differentiating intrauterine from extrauterine masses.[1] More specifically, intrauterine leiomyomata have a predictable appearance,[2,3] and the angiographic findings of extrauterine pedunculated leiomyomata are characteristic.[1,3] Although uterine leiomyomata are very vascular lesions, they derive their blood supply primarily from the uterine arteries. As with other tumors, except arteriovenous malformations, parasitic blood supply from neighboring structures has been considered a reliable sign of malignancy.[4-6] The purpose of this communication is to report a case of benign giant pedunculated uterine leiomyoma with parasitic blood supply from the superior and inferior mesenteric arteries, a situation not reported in the English literature.

From the Department of Diagnostic Radiology, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois

David J. Kurti, M.D., House Staff Adjunct Attending Radiologist, Presbyterian-St. Luke's Hospital; Instructor of Diagnostic Radiology, Rush Medical College

Suresh K. Patel, M.D., Associate Attending Radiologist, Presbyterian-St. Luke's Hospital; Assistant Professor of Diagnostic Radiology, Rush Medical College

Jerry P. Petasnick, M.D., Associate Attending Radiologist, Presbyterian-St. Luke's Hospital; Associate Professor of Diagnostic Radiology, Rush Medical College

CASE REPORT

A 22-year-old black female presented with the chief complaint of a progressively enlarging abdominal mass of one year's duration. Physical examination demonstrated a huge abdominal mass which originated in the pelvis but was distinctly separate from the uterus. Excretory urography showed elevation of both kidneys, with minimal hydro-

nephrosis; there was neither compression of the dome of the bladder nor anterior compression of the rectosigmoid.

Percutaneous retrograde transfemoral abdominal aortography and selective visceral arteriography were undertaken to further evaluate the mass. The abdominal aortogram demonstrated the mass to be hypervascular (Fig. 1). The ovarian arteries were normal. Selective right and left internal iliac artery injections (Figs. 2 and 3) demonstrated that the uterus was normal in size. The right uterine artery was in its normal position. The left uterine artery was displaced to the left. There was a very large branch of the left uterine artery seen coursing superiorly and toward the right, and it was considered that this branch was in the pedicle of the tumor. Selective superior mesenteric artery injection (Fig. 4) demonstrated elevation of the superior mesenteric artery and its jejunal and ileal branches superiorly and toward the left. Numerous tumor vessels arising from the superior mesenteric artery were seen supplying the superior portion of the mass. A selective inferior mesenteric artery injection also demonstrated parasitic blood supply, with tumor vessels supplying the left lateral portion of the mass. (Figs. 5a and 5b).

Fig. 2—Late arterial phase of selective *left* internal iliac arteriogram demonstrates large tortuous left uterine artery (arrows) with marked hypervascularity and tumor vessels.

Fig. 1—Capillary phase of abdominal aortogram demonstrates hypervascular tumor almost completely filling the abdominal cavity.

A pedunculated malignant neoplasm of the uterus, probably leiomyosarcoma or angiosarcoma, was suspected. At surgery, a large pedunculated leiomyoma of the uterus was found. There was no evidence of invasion of the mesentery or omentum. The tumor weighed 6.7 kg, and the final pathologic diagnosis was leiomyoma.

DISCUSSION

The arteriographic criteria for intrauterine leiomyomata are well established.[2,3,7,8] There is usually loss of tortuosity of the marginal segment of both uterine arteries and distortion of the

intramural branches. The uterus is enlarged and there is lateral displacement and usually bilateral enlargement of the marginal portions of the uterine arteries. Typically the tumor is quite vascular, especially in young females, and tumor vessels are often seen with larger leiomyomas.

With pedunculated leiomyomas, the features are somewhat different. The pedunculated leiomyoma characteristically receives the majority of its blood supply from a single uterine artery, and there is also unilateral dilatation of the parametrial and marginal portions of the uterine artery.[1,3,9] The fundal branches at the base of the pedicle are also enlarged and tortuous. The uterus is of normal size. The appearance of the tumor itself is identical to intrauterine leiomyomas with hypervascularity, tumor vessels, and often a "stain" on delayed films. The main differential diagnostic concern is the exclusion of an adnexal hypervascular tumor. Selective internal iliac arteriography allows this differentiation to be made, since extrauterine masses usually obtain their blood supply from adnexal branches of the uterine artery rather than from the uterine artery itself, as seen with pedunculated leiomyomas.[1] There are no reports of an ovarian artery supplying a pedunculated leiomyoma.

In several series of arteriographically demonstrated leiomyomas, there has been no mention of parasitic blood supply. In fact, tumors of any tissue exhibiting parasitic blood supply are unusual, except that hypernephromas extending out of the renal capsule not infrequently obtain blood supply from nearby retroperitoneal arteries. Sondag, *et al.*,[5] described three cases of hypernephroma in which blood supply was obtained from the inferior or superior mesenteric arteries, and concluded that this was a reliable sign of invasion of the mesentery. Ruzicka, *et al.*,[4] demonstrated a case of retroperitoneal lymphosarcoma with parasitic blood supply from the superior mesenteric artery and invasion of the mesentery, and a case of hypernephroma with parasitic blood supply from the left gastroepiploic artery with invasion of the omentum.

Fig. 3—Late arterial phase of selective *right* internal iliac arteriogram shows normal right uterine artery (arrows). Visceral branches of the right internal iliac artery supply the hypervascular tumor.

According to Ruzicka,[4] parasitic blood supply may occur in two ways: Either

A) the lesion directly invades a contiguous structure,

or

B) the terminal branches of the main artery supplying the lesion anastomose with branches of a nearby second artery.

With direct invasion, selective injection of the parasitized artery will show tumor

Fig. 4—Selective superior mesenteric arteriogram demonstrates displacement of the superior mesenteric artery (arrow) upward and to the left. Tumor vessels are seen in the upper portion of the mass.

vessels in its distribution. If there are anastomotic communications without actual invasion, selective injection of the parasitized artery shows an enlarged artery with normal vascular pattern in its own region of distribution, but abnormal vascularity may be seen in the terminal branches supplying the lesion. Sprayregen[6] recently reported three cases of parasitization of blood supply with malignant tumors, but without actual invasion of the neighboring structures. He stresses that derivation of the blood supply from adjacent structures is not a reliable sign of tumor invasion into that structure.

In the case presented, selective internal iliac arteriography demonstrated findings typical of a pedunculated leiomyoma. It is well known that uterine leiomyomas have abundant capsular vessels, and often these may be demonstrated arteriographically as nontortuous, arched blood vessels at the periphery of the lesion.[3,7,9] We hypothesize that vascular communications were established in this case through capillary adhesions between the capsule of the leiomyoma and the mesentery. Parasitic blood supply is not specific for malignant lesions and can occur with leiomyoma, and possibly with other hypervascular tumors as well.

Fig. 5a.—Selective inferior mesenteric arteriogram shows tumor vessels arising from branches of the inferior mesenteric artery.

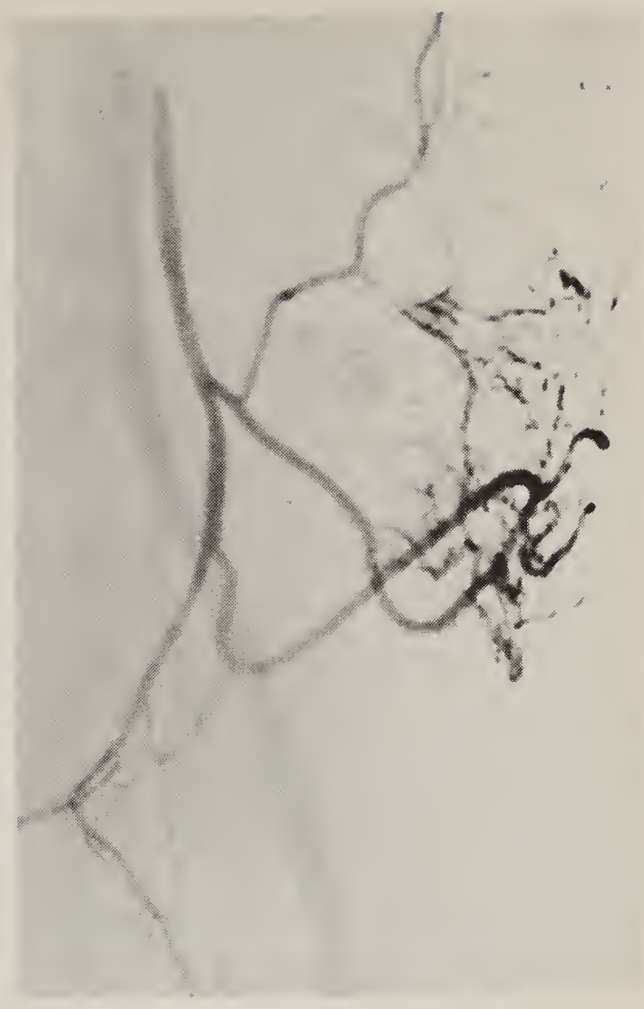


Fig. 5b.—Subtraction film from the inferior mesenteric arteriogram shows the abnormal vasculature to better advantage.

REFERENCES

1. Altemus R: Differentiating uterine and extra-uterine masses by bilateral selective hypogastric arteriography. Radiology **92**:1020, 1969

2. Borell U, Fernstrom I, Lindblom K, Westman A: The diagnostic value of arteriography of the iliac artery in gynecology and obstetrics. *Acta Radiol* (Diagn) **38**:247, 1952

3. Fernstrom I: Arteriography of the uterine artery. Its value in the diagnosis of uterine fibromyoma, tubal pregnancy, adnexal tumor, and placental localization in cases of intra-uterine pregnancy. *Acta Radiol* (Suppl) 122, 1955

4. Lang EL: Arteriography in gynecology. Radiol Clin N Amer **5**:133, 1967

5. Meng C, Elkin M: Gynecologic angiography. Semin Roentgen **4**:267, 1969

6. Radberg C, Wickbom I: Pelvic angiography and pneumoperitoneum in the diagnosis of gynecologic lesions. *Acta Radiol* (Diagn) **6**:133, 1967

7. Ruzicka FF, Rossi P, Abrams RE, Tracht DG: Anomalous and parasitic blood supply in the abdomen. Radiology **96**:216, 1970

8. Sondag TJ, Petasnick JP, Patel SK, Alcorn FS: Hypernephromas with parasitic blood supply from the superior and inferior mesenteric arteries. Radiology **103**:509, 1972

9. Sprayregen S: Parastic blood supply of neoplasms, mechanisms and significance. Radiology **106**:529, 1973

DEAR DR. BRAINARD—
A LETTER TO THE FOUNDER OF RUSH MEDICAL COLLEGE

Robert J. Glaser

About a month ago, on a Sunday afternoon, I went to my office to pick up a book that I had forgotten to put in my briefcase when I left the previous Friday afternoon. I needed the book in connection with some work I wanted to complete in preparation for a meeting on Monday morning—hence the special trip back to the office.

As I approached my desk to pick up the book in question, I saw an envelope in the "In" tray on the corner of the desk. I knew it hadn't been there when I left on Friday because for the first time in months I had disposed of all my correspondence and had left the tray for incoming mail absolutely empty! Curious about the envelope, I picked it up and noted that it was hand addressed to me, though only with my name. Further, the script was rather distinctive and reminiscent of that used long ago—I remember my reaction, which was that the envelope had been addressed in a far earlier day.

I began to wonder how the letter got to my desk. Our building is locked over the weekend, and I knew that none of my colleagues had been in the office since we all left on Friday. Further, this letter clearly had not come through the postal system.

The whole business struck me as more than unusual, but when I opened the envelope, took out the letter contained therein and hurriedly read it, I realized that *unusual* was hardly the appropriate word to describe the situation! Let me read you the letter and you will see what I mean. The letter was written in the same flowery, somewhat ancient hand as was my name on the envelope, and it began as follows:

Dear Dr. Glaser:

You will no doubt be surprised—or shall I say even mystified—to hear from me. We have never met, of course, and if all goes well with you, and I trust it will, it may be some time till we see one another. You may not even know of me but that is unimportant. What is important is that I ask of you a favor that I hope you will be disposed to grant. By means which I shan't go into here, I learned that you will be speaking at the 99th commencement exercises of the Rush Medical College, and their first since the medical program was reestablished. As Rush is an institution I founded, you can understand that I still feel very close ties to it. I wondered therefore whether you would be kind enough to report to me, at your convenience, on the state of the

Robert J. Glaser, M.D., President, Henry J. Kaiser Family Foundation, Palo Alto, California; Consulting Professor of Medicine, Stanford University School of Medicine, Stanford, California.

Commencement address, delivered at the 99th Commencement Exercises of Rush Medical College, Chicago, Illinois, June 15, 1973, at Orchestra Hall

College and its programs, and advise me as to whether the high expectations we held for the College initially are still justified. My last direct contact with Rush was on October 10, 1866, when I fell victim to a malady that we called the cholera. I have chatted briefly with a relatively new arrival here called Abraham Flexner, and he said that when he saw the College in 1910 it looked promising and stood quite in contrast with most of the others he visited during the course of a tour of all the medical schools operating at that time.

But I gather the Medical College has entered on a new era, and I therefore entreat you, Dr. Glaser, to advise me as to its status. I am told you have been Dean of two medical schools and even though I understand that a Dean is someone who is not smart enough to be a professor, I will take a chance and rely on your judgement.

For your help I offer in advance my profound thanks.

The letter was signed "Your obedient servant, Daniel Brainard, M.D."

By the time I finished reading the letter, I was taken aback, as you will understand. For a fleeting moment I wondered how Dr. Brainard knew where my office was, but after reflecting on the fact that he knew I was to speak at the Rush Commencement, I could only conclude that his informational sources were adequate. In any case, after due deliberation, I decided to comply with his request. Consequently, over a period of a week or so, I prepared a reply to Dr. Brainard's inquiry. Let me share with you what I wrote. It went as follows:

Dear Dr. Brainard:

I am sorry not to have replied sooner to your letter. As you no doubt can understand, I hadn't expected to hear from you. Further, although being a foundation officer is a rather more restful occupation than being a dean, I do find it keeps me busy trying to give away money. Then, too, writing commencement addresses takes time, and as I have to prepare one for the upcoming graduation of the first class of the reactivated Rush Medical College, I have been fully occupied.

I do, however, want to try to provide you with the information you requested, and hope you will find it both interesting and gratifying.

I hardly know where to begin. As you undoubtedly realize, in the 107 years that have elapsed since you fell ill and succumbed to the cholera, a great deal has happened—not only to Rush but to medicine and society in general. In medicine, knowledge has expanded in a spectacular way.

For example, in the field of infectious diseases, which were so troublesome to you and your colleagues, we now have identified the cause of many maladies, have learned to prevent some and to treat effectively a goodly number of the remainder. In fact, your death occurred just about the time that what we call the "Golden Age of Bacteriology" began. It was a period in which our understanding of bacterial affections greatly increased. The cause of cholera, the illness that felled you so suddenly, was discovered by a remarkable German scientist, Robert Koch, just 17 years after you departed. He also, incidentally, identified the tubercle bacillus. Inasmuch as cholera depletes the body of fluid and electrolytes with alarming rapidity, its treatment requires prompt and massive replacement of both the parenteral route: you clearly had no such therapy available at the time of your encounter with the cholera vibrio, and the sad result was thus predictable. Although cholera is still a problem in some parts of the world —particularly Africa and the Far East— you'll be glad to know that Chicago is free of it, and has been for a good many years. The last time anyone got into trouble from drinking the water in Chicago was in 1933 during the World's Fair when a bit of a mix-up between the water and sewer lines in a hotel resulted in some cases of amebiasis, but that was

corrected promptly, albeit not without having stirred things up a bit.

But I am getting ahead of the story. I have already alluded to the fact that we have made enormous progress in the century since you departed this sphere. In every field of human endeavor the hallmark has been growth. I want to concentrate primarily on biomedical science in this letter, but I digress long enough to tell you that the Indian pony on which you rode into Chicago in 1836 would find the city a rather uncongenial place today. The horse and carriage have been displaced by the automobile, and although in the rush hour it may take as long or longer to traverse the city by car as it did in your time by pony, that is merely the price of progress. We also now must contend with something we call pollution—different from the pollution of your day, which was mostly due to unseen infectious agents. Ours is made up of noxious particles and toxic gases, which generate a miasma we call smog. Smog contributes to enhanced patient loads in the pulmonary disease clinic at the Medical Center—a contribution we could do without. It may be that the oil shortage we now face may render our cars less operative. In that case, smog will decrease, and many of us will learn to do a bit more walking. That in turn might improve cardiac function and decrease the incidence of a very troublesome entity called coronary artery disease, which I should note, was characterized by a distinguished physician on the Rush-Presbyterian roster, Dr. James B. Herrick.

But there I go again, Dr. Brainard, getting ahead of my story. What I should note at this juncture is that your medical college grew in stature and distinction through the late 19th and early 20th centuries. In collaboration with the Presbyterian Hospital, more than 10,000 physicians were trained for a growing America. The staff distinguished itself in many fields of medicine.

You mentioned Abraham Flexner in your letter to me. One of Flexner's key points in the famous report that bears his name was the importance of a university affiliation for medical schools. It bears noting that Rush actually had an affiliation with Lake Forest University as early as 1887. More important, only seven years after the founding of the University of Chicago, destined to be one of the country's great institutions of higher learning, Rush became an affiliate, and in 1923 became an integral part of the University. This relationship persisted until 1941. At that time, a separation occurred, but, wisely, the corporate existence of Rush was maintained, and its staff became an important unit of the medical education program at the nearby University of Illinois.

In a sense, one can only think of Shakespeare's wise aphorism—"What is past is prologue." As an aside I am moved to relate a story that has to do with a friend of mine who noted that quotation on a statue outside the National Archives Building in Washington. He asked the taxi driver with whom he was riding what his interpretation of the quotation was, and the reply came back promptly: "You ain't seen nothing yet." Well, that's the way it is with the Rush Medical College, Dr. Brainard.

You see, we have got ourselves into some serious difficulties in this country during the past 50 years, in no small measure due to the progress we have made. By this I mean that our great progress has in effect been a two-edged sword. In every field of human endeavor we have moved forward, but in most instances there have been unfortunate by-products. In some cases, the situation is far more than unfortunate.

For example, the field of physics underwent a remarkable revolution at the beginning of this century, and as a result we came to a detailed understanding of the structure of matter. In turn, chemistry and biology entered a new era wherein it became possible to bring new definition to normal and abnormal biochemical and physiological function. Entire new fields such as molecular biology have come to the forefront, and genetics has moved to a place of key importance

in medicine. Yet, with all these marvelous advances, there is the terrible spectre always before us of the destruction of civilization because that same series of advances in physics and chemistry ultimately eventuated in what we call nuclear weapons; these are capable of destructive forces that can only terrify one if he thinks about them. Sad to relate, they could destroy all of civilization.

I am sorry to have to add such a depressing note, Dr. Brainard, but I feel obliged to try to convey to you the complexities of the age in which we live. Nonetheless, I keep getting away from the main purpose of my letter, which is to report on the status of Rush Medical College in 1973.

As one of the early pioneers in research, you obviously appreciated the necessity of adding new knowledge to medicine. So did an increasing number of those in medicine, particularly after the revitalization of American medical schools stimulated by our mutual friend, Flexner.

In the early part of the 20th century biomedical research was still a modest enterprise, supported by a few philanthropic organizations like the Rockefeller Foundation and the Commonwealth Fund, but after the massive military conflagration we call World War II, and in large measure because of some striking medical advances that were made in the course of that conflict, biomedical research came into its own. Would you believe, Dr. Brainard, that a substance produced by the common penicillium mold, aptly called penicillin, reversed in a matter of hours, as if by magic, the course of a multitude of hitherto life-threatening infections such as those due to streptococci and pneumococci? Or that the loathsome affliction called syphilis could be cured in a short period of time by this same substance, which we call an antibiotic? Well, Dr. Brainard, I kid you not! And this is only a tiny sample of what is now available in the medical armamentarium. I shan't detail them for, in the parlance of the day, I don't want to "blow your mind." What I do want to emphasize is that in a matter of two decades the people of this country saw medical research blossom at a massive rate. In turn, they took a new view of medical care—no longer did they consider it a privilege of the few. Rather, they now look on it as the right of the many. The net result, to compress a rather complex story into simple terms, was the recognition of what is now commonly called a health care crisis. It has a number of components:

1) The need for many more physicians and other health care personnel to provide the unmet demands of a growing and medically more sophisticated population.

2) The updating of medical and other curricula in the health field to make the educational process more efficient and effective while insuring its quality.

3) The more effective use of health facilities so that health care delivery can be expanded in a manner that meets the needs of different segments of our society.

There are many facets of these issues that could be delineated, but this letter is getting too long, so I'll forego them for the present. What I do want to do, Dr. Brainard, is to tell you how your institution has responded to the major problems I have outlined.

I have already noted that the Rush charter was maintained after the University of Chicago affiliation was terminated, and reported how the Rush-Presbyterian-St. Luke's group became a major teaching unit of the University of Illinois Medical College. I am sure you realize this all didn't happen by chance. But one of the reasons it did is that the trustees had the wise judgment to bring a bright young man called James Campbell here from Albany. It just occurs to me that you came to Chicago from the State of New York and, lo and behold, so did Campbell. I don't think he came on a pony although when he and I were medical school classmates, he did enjoy "horsing around." But for Rush-Presbyterian-St. Luke's the "Campbells are coming" was a good omen. Everything has been full speed ahead ever since. I

don't know if there was a Mrs. Brainard but I can tell you that there is a Mrs. Campbell and she has been a great partner in this enterprise.

Of course, no one ever does a major job all by himself, and what has happened here reflects the dedicated devotion of many people. Without an enlightened and venturesome Board of Trustees, the reincarnation of Rush would not have occurred. The academic leadership of Mark Lepper as Dean and the contributions of all the other able men and women who make up the academic and non-academic ranks were essential components.

The main point is that this institution has not only moved with the times but in fact has been in the forefront. The consolidation of the Presbyterian and St. Luke's Hospitals, and the creation of the Rush-Presbyterian-St. Luke's Medical Center, culminating in the reactivation of the Rush charter in 1971, represented the orderly and well planned evolution of an educational enterprise of excellence. The establishment of the Rush College of Nursing and Allied Health Sciences and the Rush Graduate College further embellish that enterprise.

The designation of the entire Chicago center as Rush University, and its cooperative program with a group of outstanding midwestern colleges, is a model that I hope will be emulated elsewhere. The improvement in the quality of education and science in our secondary schools and many of our undergraduate colleges provides a means of shortening the span of medical education and avoiding redundance while maintaining the highest academic standards. Here, as in other areas, Rush has taken advantage of this development, and is in the vanguard in adapting it for the benefit of society.

Although all of this should make you swell with pride, Dr. Brainard, that's not all of the story, for in forceful and creative fashion your old institution has also tackled the problem of improving health care delivery, and doing so in ways that will make it more efficient.

Even before the reactivation of Rush Medical College, the Mile Square project, under Dr. Joyce Lashof's leadership was one of the first efforts in the country to do something for the health care of the disadvantaged poor in an urban slum. I emphasize that this project was begun before such ventures became popular and it reflects great credit on the institution that made it possible.

Now, with the advent of the medical school, a network of affiliated hospitals in the city and in outlying areas is being developed to serve one-and-a-half million people. This network, utilizing the highly sophisticated and technologically advanced facilities of the Presbyterian-St. Luke's Hospital as a back-up, again represents a model that I hope will be widely emulated in this country. Not only does it promise a higher standard of health care to a multitude of our citizens, but it will also provide a diversity of educational experiences for students in medicine and the allied health fields, and will serve as an effective base for the continuing education programs that the rapid advances in knowledge make mandatory.

Well, Dr. Brainard, there are lots of things I haven't said, but I hope what I have told you gives you a reasonable picture of what has happened to that tiny little medical school that you brought into being in 1837 when its charter was issued by the Illinois legislature.

As I write this letter, I have before me your 17th Annual Catalogue, dated 1859. I could not find an earlier one out here on the West Coast where I live. Perhaps you sent earlier copies out but I realize that the postal service in your time was a bit irregular. Incidentally, having told you about all our progress, I should say that the postal service should be excluded —it takes about the same amount of time for mail to reach the Coast now as it did 100 years ago.

In any case, I note that a summary of your first 16 classes indicates that of 1591 who matriculated, only 468 graduated. You'll be pleased to know that the students of Rush reincarnate have a far

more creditable record. Of the 33 students who entered the third year in 1971, 32 are graduating. As of the coming fall, 70 students will be admitted each year, and without doubt, the number graduating will approximate that number. It will surprise you to know that of the 66 members of the class who entered in 1971, 11 were women. I suspect "women's lib" is not a phrase that is familiar to you, Dr. Brainard, but you will, I trust, be pleased to know that women are now more appropriately represented in medicine and many other fields and are strengthening all of them significantly.

Back in 1859, I counted 10 professors and 1 janitor on the roster. Today it takes 30 printed pages to list the faculty! Your 15-page catalogue has grown into a very large volume.

What is really important, however, is not size *per se* albeit today's medicine requires space and budget of a magnitude beyond your comprehension. What matters, Dr. Brainard, is that the Rush Medical College, a pioneer in medical education in the 1840's, is once again a pioneer in the 1970's. It is an institution true to its proud heritage, and it is about to graduate an able group of young men and women who will take their place in our complex society, to minister to the sick just as did their medical forebears more than a century ago. They have had an exceptional opportunity to learn the art and the science of medicine, both of which are essential to the good physician.

Well, Dr. Brainard, the hour is late, and it is time for me to begin to write the address I am to give at the Rush Commencement. I hope the foregoing will have been interesting to you; I am delighted to have had this opportunity to provide you with a report on the Rush Medical College.

I will attach here the catalogue of the Medical College, and the other pertinent documents to which I referred. You can peruse them at your leisure.

With all warm regards, I remain

Very sincerely yours,
Robert J. Glaser, M.D.

Dr. Brainard had neglected to provide me with the proper address to which I should send my reply, and indeed, even had he supplied the address I am not sure what mode of transport would have been in order to get the letter to him. And despite the fact that I am certain he is an estimable man, I clearly had no desire to meet with Dr. Brainard personally in order to deliver my letter.

Then I hit upon what proved to be a capital idea. Before I left my office on a Friday afternoon several weeks ago, shortly after I finished the letter, I put it in an envelope, simply addressed to Dr. Daniel Brainard, and placed the envelope in the box for outgoing correspondence, adjacent to the "In" tray where I had found Dr. Brainard's letter. And guess what—on the following Monday morning, when I reached the office, the letter was gone! I assumed that to be the end of my current contact with Dr. Brainard. But *mirabile dictu*, when I arrived in Chicago and checked in to my hotel yesterday afternoon, the room clerk asked if I expected any mail or messages. Before I had time to reply, he began thumbing through the accumulated file, and shortly handed me an envelope, yellowed like the one I had found on my desk a month earlier. It bore my name in the same old fashioned script as well as the direction, "hold for arrival on June 14th." Needless to say, this time I knew whence it came. When I got to my room, I opened Dr. Brainard's letter, read it, and now want to share it with you. He had written the following:

Dear Dr. Glaser:

Thank you very much for your report. I do appreciate your preparing it for me, and assure you I am highly pleased to know what an illustrious institution has grown up on the modest base I established so long ago. I want you to know I read the entire catalogue from cover to cover!

Although my hopes and expectations were high back in 1837 when our charter was obtained, the outcome has exceeded my wildest dreams.

I do hope you enjoy the Commencement and would be grateful if you would extend my felicitations to Mr. Blettner, Mr. Dick, and the Board of Trustees, to Dr. Campbell, Dr. Lepper and the Faculty, and especially to the students. I presume you will deliver a brief *l'envoi* to them, and would consider it a favor if you would be willing to associate me with your comments.

Thank you again, Dr. Glaser. I wish you well.

Your obedient servant,
Daniel Brainard, M.D.

That then is the end of the story of my report to Dr. Brainard, the founder of Rush. There is left only a brief personal word to the Class of 1973. And, as per his request, I speak on behalf of Dr. Brainard and myself.

We congratulate the class of 1973 on the successful completion of the arduous and demanding requirements that you have met en route to your M.D. degree. We welcome you to the fellowship of educated men and women, with the privileges and responsibilities that pertain thereto. It is written in Ecclesiasticus, "For of the most High cometh healing"—and all of you who receive your degrees today will have the unique privilege of serving your fellows in their time of need. That you will do so with the compassion, dedication and competence of the good physician I have no doubt.

You will have the serious responsibility of being perpetual students. Henry Gray, whose *Anatomy* I am sure you still remember from your first year, so described himself when, at the age of 18, he entered St. George's Hospital to devote his all-too-short life to medicine. In terms of the times in which he lived, he made enormous contributions. But given the medical armamentarium that is yours, you can do things for the sick that Gray never dreamed of. I admonish you to remember, however, how rapidly medicine advances these days; consequently just as the magnificent edifice of the modern Rush has been built on the foundation that Dr. Brainard began in 1837, so you must build continually on the fine educational foundation you have been given at Rush.

Finally, for Dr. Brainard and myself, let me bid each of you a long, healthy and happy life in medicine and wish you Godspeed.

ABSTRACTS

OF PUBLICATIONS BY THE STAFF

Gastroenterology

Franklin JL, Rosenberg IH: Impaired folic acid absorption in inflammatory bowel disease: Effects of salicylazosulfapyridine (Azulfidine). *Gastroenterology 64:517, 1973*

Review of patients hospitalized for inflammatory bowel disease at the University of Chicago (Billings) Hospital revealed a high prevalence of folate deficiency as evidenced by low serum folates (63 percent) and macrocytosis (10 percent). Absorption studies utilizing tritiated folic acid in patients with ulcerative colitis and granulomatous colitis revealed impaired absorption of monoglutamic folate. Analysis of absorption studies performed sequentially on and off Azulfidine indicated further reduction in folate absorption associated with administration of this drug. Oral folic acid tolerance tests confirmed the observation that Azulfidine impaired intestinal folate absorption. *In vitro* experiments with isolated rat intestine have shown that the inhibitory effect is specific for salicylazosulfapyridine and not seen with its primary cleavage products sulfapyridine and 5-aminosalicylic acid. The malabsorption of folic acid is presented as another facet of jejunal dysfunction seen in inflammatory bowel disease. Surveillance of folate status and correction of subclinical folic acid deficiency may be important in the treatment of these patients.

Microbiology

Falk L, Deinhardt F, Wolfe L: Transformation *in vitro* of nonhuman primate lymphocytes by Epstein-Barr virus. *Clin Res 20:793, 1972*

Epstein-Barr virus (EBV), a herpes-type virus, causes infectious mononucleosis (IM) and has been implicated as the etiologic agent of Burkitt's lymphoma (BL) and nasopharyngeal carcinoma (NPC). Lymphocytes from IM patients and cells from BL and NPC frequently yield lymphoblastoid cell-lines after cultivation, and EBV is always associated with these cell-lines.

Peripheral squirrel and marmoset lymphocytes (recipients) were transformed *in vitro* into lymphoid cell-lines after cocultivation with lethally irradiated (6000 r), EBV-carrying human lymphoid cells (donor). The monkey lymphocytes became established as cell-lines after 25 to 35 days of cultivation; donor and recipient lymphocytes, cultured separately, failed to form cell-lines. Chromosomal analyses of the cell-lines revealed normal diploid squirrel monkey and marmoset karyotypes. EBV antigens were demonstrated in the monkey cell-lines by immunofluorescent staining. These results confirm and extend previous reports of transformation by EBV of lymphocytes from squirrel monkeys and marmosets (Miller *et al.*, PNAS 69:383, 1972) and gibbons (Henle, unpublished data). Despite the proven susceptibility of marmosets to various oncogenic viruses, experimental infection with EBV has not succeeded, but attempted infection with EBV transformed autologous lymphocytes has not been investigated. The transformed lymphocytes have been inoculated into the autologous monkeys, and their clinical and immonological responses were studied.

Froesner GG, Peterson DA, Deinhardt F: Comparison of IEOP, RCA and RIA for the detection of hepatitis B antigen. *Abstracts of the Annual Meeting, Amer Soc Microbiol, 1973*

The sensitivity of immunoelectroosmophoresis (IEOP, Ortho Diagnostics), solid phase radioimmunoassay (RIA, Abbott Lab.) and red cell agglutination (RCA, Abbott Lab.) was compared by examination of: 1) dilutions of serum containing hepatitis B antigen (HB ag) of known subtypes; 2) a test panel from the Division of Biologics Standards, NIH; 3) sera of 200 autpatients with a tentative diagnosis of hepatitis; and 4) sera of 1661 volunteer blood donors. The sensitivity for subtype ad was RIA (1), RCA (1/2), IEOP (1/256) and for subtype ay: RCA (1), RIA (1/8), IEOP (1/128). Evaluation of the Division of Biologics Standards' test panel demonstrated HB Ag in 34 of 60 samples by RIA, 33 by RCA and 25 by IEOP. HB Ag was detected in 57.5 percent (115/200) of the outpatients with RIA, 54 percent (108/200) with RCA and in 42.5 percent (85/200) with IEOP. In screening volunteer blood donors 0.78 percent (13/1661) of the sera were positive by RIA, 0.66 percent (11/1661) by RCA and 0.18 percent (3/1661) by IEOP. These results indicate that RIA and RCA are much more sensitive than IEOP in detecting HB Ag. The RCA test appears highly sensitive, unspecific positive results occur only rarely, it is easily performed, it does not require expensive equipment, and it could readily be used for routine testing.

Johnson TR,Massey RJ, Deinhardt F: Lymphocyte and antibody cytotoxicity to tumor cells measured by a micro-^{51}chromium release assay. *Immuno Communic 1:247, 1972*

^{51}Chromium release micro-assays for both lymphocyte and antibody cytotoxicity have been developed. Tests versus several different types of target cells can be performed on one to five ml of blood. The results are objective, highly reproducible, and can be obtained within six hours. Application of this test system to primates carrying tumors induced by various oncornaviruses has shown highly specific response, *i.e.*, the animals developed lymphocyte and antibody cytotoxicity against cells transformed by the same virus which had induced their tumors but they remained non-reactive against cells transformed by other viruses.

Marczynska B, Falk L, Wolfe L, Deinhardt F: Transplantation and cytogenetic studies of *Herpesvirus saimiri*-induced disease in marmoset monkeys. *J Natl Cancer Inst 50:331, 1973*

The response of marmosets to transplanted tumor tissues from *Herpesvirus saimiri* (HVS)-infected marmosets was studied. Recipient marmosets developed lymphoproliferative disease indistinguishable from the disease produced in marmosets by experimental infection with cell-free HVS. Clinical features of the disease in recipient marmosets were similar to those found earlier: HVS was isolated from peripheral lymphocytes by co-cultivation methods, all marmosets developed HVS serum antibodies, and marmosets died from their disease 26 to 67 days post-inoculation. Cytogenetic analysis of peripheral leukocytes of recipient marmosets indicated that the lymphoproliferative disease was a result of transformation *in vivo* of recipient lymphocytes and not of growth of donor tumor cells. Chromosomal analysis of hematopoietic chimeric marmosets, inoculated with tumor tissues or cell-free virus, suggested that the HVS-induced neoplastic disease was multiclonal in origin.

Massey R, Wolfe L, Deinhardt F: Characteristics of marmoset cell-lines transformed by various oncornaviruses. *Abstracts of the Annual Meeting, Amer Soc Microbiol, 1973*

Some species of marmosets, South American monkeys, are highly susccptiblc to Rous sarcoma virus, SR-RSV; feline sarcoma virus, FeSV; and simian sarcoma virus type 1,

SSV-1. The *in vitro* susceptibility of cell-lines derived from skin or muscle biopsies of marmosets of various ages to these three oncornaviruses was studied. Each virus induced foci of transformed cells in which the morphology of the focus was characteristic of the virus. The efficiency of transformation was not dependent on the age of the marmoset used for the biopsy. The RSV and FeSV transformed cells formed colonies in soft agar and could be grown in suspension culture. The RSV transformed cell-lines contained avian group specific (gs) antigen as detected by indirect immunofluorescence; however, infectious transforming virus could be detected only in some of the RSV transformed cell-lines by fusion with chicken embryo fibroblasts. FeSV and SSV-1 transformed cell-lines contained oncornavirus gs antigens, and infectious virus could be detected in the medium. The FeSV and SSV-1 transformed cell-lines were tumorigenic for autologous and homologous marmosets; the RSV transformed cell-lines were tumorigenic only in autologous animals.

Peterson DA, Froesner GG, Deinhardt F, Holmes AW: The incidence of hepatitis B antigen and antibody in various populations. *Abstracts of the Annual Meeting, Amer Soc for Microbiol, 1973*

The sera from populations with different exposure levels to hepatitis B antigen (HB Ag) were tested for HB Ag by immunoelectroosmophoresis (IEOP, Ortho Diagnostics), radioimmunoassay (RIA, Abbott Lab.) and red blood cell agglutination (RCA, Abbott Lab.) and for hepatitis B antibodies (HB Ab) by hemagglutination (HA, Virgo Reagents). HB Ag was detected in 3.3 percent (3/91) of workers processing human plasma and 79 percent (72/91) had HB Ab. Workers having indirect contact with plasma processing had no HB Ag but 53 percent (34/64) had HB Ab and workers with no contact had no HB Ag, yet, 15 percent (8/51) had HB Ab. A similar correlation between exposure to hepatitis and incidence of HB Ag and HB Ab was also shown in hospital staff members. In volunteer blood donors HB Ag was detected in 1.22 percent (24/1959) and HB Ab in 6.4 percent (48/755); 57 percent (115/200) of outpatients with suspected hepatitis demonstrated HB Ag while 31 percent (62/200) exhibited HB Ab; 47 percent (125/263) of patients hospitalized with clinical hepatitis had detectable HB Ag. The persistence of HB Ag and the development of HB Ab was examined. The incidence of HB Ag and HB Ab showed a marked correlation with the level of exposure to HB Ag in all populations. Nearly the same percentages of sera were positive by RIA and RCA, whereas IEOP detected as few as 12 percent and as many as 74 percent of RIA positive sera in different groups.

Peterson DA, Wolfe LG, Deinhardt F, Gajdusek DC, Gibbs CJ Jr: Transmission of kuru and Creutzfeldt-Jakob disease to marmoset monkeys. *Abstracts of the Annual Meeting, Amer Soc for Microbiol, 1973*

Kuru and Creutzfeldt-Jakob disease (CJD), chronic degenerative diseases of the central nervous system have been transmitted experimentally to several species of nonhuman primates, but only after incubation periods of nine months to more than three years. In this study, two marmosets (*Saguinus oedipus*) inoculated intracerebrally when eight months old with 10 percent brain homogenates prepared from two human kuru patients and one marmoset (*S. fuscicollis illigeri*) inoculated when six months old with a CJD brain suspension died with characteristic spongiform encephalopathy 21, 38, and 43 months after inoculation respectively. Incoordination, tremors, and impairment of vision were observed one to eight days prior to death. Ten-percent brain homogenates from marmosets with experimentally-induced kuru were inoculated intracerebrally into neonatal marmosets (*S. nigricollis, S. fuscicollis*); the incubation periods in second and third serial marmoset passages were reduced to one-and-one-half, two, and nine months respectively in three animals of passage 2, and to one-and-one-half and two months in two animals of passage 3. Cell cultures were established from brain tissue of all infected animals; a variety of morphologic changes were observed but their significance, if any, has not been determined.

Wolfe LG, Smith RD, Hoekstra J, Marczynski B, Smith RK, McDonald R, Northrop RL, Deinhardt F: Oncogenicity of feline fibrosarcoma viruses in marmoset monkeys: Pathologic, virologic, and immunologic findings. *J Natl Cancer Inst 49:519, 1972*

Two strains of feline fibrosarcoma virus, Snyder-Theilen (ST-FeSV) and Gardner-Arnstein (GA-FeSV), consistently induced undifferentiated sarcomas or fibrosarcomas in marmoset monkeys, *Saguinus fuscicollis*, *S. nigricollis*, and *S. oedipus*. The invasive neoplastic disease was characterized by a progressive course and death one to six months after inoculation. Metastases to lung and regional lymph nodes were observed in 20 percent of the animals. Sarcomas induced by cell-free virus (primary tumors) contained group-specific (gs) antigen but no demonstrable C-type virus; complete infectious virions were produced after these tissues were explanted *in vitro* or were inoculated into susceptible hosts *in vivo*. Cell-lines established both from primary and serially transmitted tumors produced C-type virus that was oncogenic in marmosets and cats. The serially transmitted marmoset tumors, composed primarily of recipient cells, contained C-type virus, and a cell-free extract of one of these tumors induced transformation of cat embryo cells *in vitro*. Gs antibodies were detected in the serum of 70 percent of the tumor-bearing marmosets that had post-inoculation courses of six weeks or longer.

Wright J, Falk L, Deinhardt F: Interferon production by marmoset continuous lymphoblastoid cell-lines. *Abstracts of the Annual Meeting, Amer Soc Microbiol, 1972*

Interferon (IF) production by six continuous lymphoblastoid cell-lines, derived from marmoset tumors experimentally induced with *Herpesvirus saimiri* (HVS) was studied. The HVS lymphoblastoid cell-lines have properties similar to the Epstein-Barr virus carrying cell-lines established from Burkitt's tumors and peripheral lymphocytes from infectious mononucleosis patients. Four of the six HVS cell-lines produced measurable levels of IF (4-512 units/4ml) as determined by plaque reduction assay on Vero cells with vesicular stomatitis virus. No correlation was shown between IF production and expression of viral functions, i.e., production of infectious virus and synthesis of viral antigens. Species specificity, broad antiviral activity and physicochemical characterization confirmed the substance as being IF. Interfering activity was measurable on marmoset, African green, rhesus and human embryonic cell cultures but not on rabbit kidney cells. IF was tested and effective against vaccinia and Newcastle disease viruses. The IF was unaffected by acid dialysis (pH 2.2), heating at 56°C for one hour, and was non-sedimentable (100,000 X g). Heating at 80°C for one hour and treatment with trypsin destroyed IF activity. The molecular weight of the IF was determined to be approximately 26,000 by column chromatography.

Obstetrics and Gynecology

Goldston WR, Johnston WW, Fetter BF, Parker RT, Wilbanks GD: Clinicopathologic studies in feminizing tumors of the ovary. *Amer J Obstet Gynec 112:422, 1972*

Clinical and pathologic data from a series of 41 patients with granulosa cell tumor are reviewed. An attempt is made to correlate these data with basic research data which relate to the pathogenesis, pathophysiology, and experimental production of these tumors. The pathologic factors related to survival are the degree of anaplasia of the tumor and the stage of the disease. The treatment of choice is complete surgical extirpation of the internal genitals, followed by irradiation in cases beyond Stage I. Conservative operation is justified only in patients with Stage I disease, who desire further childbearing. On the basis of animal experiments, it appears that postoperative estrogen administration may be useful adjunctive therapy, and this is recommended.

Goldston WR, Wilbanks GD, Campbell JA: A granulosa cell tumor in tissue culture. *Amer J Obstet Gynec 114:652, 1972*

Normal and neoplastic human granulosa cells were grown in tissue culture and observed directly and by still photography and cinematography. Morphology, growth characteriestics, and mitoses were observed, and no differences were detected between the normal and neoplastic cells. Progesterone was produced up to 21 days after granulosa tumor cells were cultured. The assay was negative after the twenty-first day. The cells were found to have a limited time of reproduction in tissue culture; this was the same in normal and neoplastic cells. Only very rare mitoses were seen after the twentieth day in tissue culture. No cell-line was established.

Misenhimer HR, Margulies SI, Panigel M, Ramsey EM, Donner MW: Effects of vasoconstrictive drugs on the placental circulations of the rhesus monkey: A preliminary report. *Invest Radiol 7:496, 1972*

This pilot study of the effect of L-epinephrine, 5-hydroxytryptamine, and vasopressin on placental circulation suggests that administration of each of the drugs results in reduced maternal uteroplacental circulation. This effect appears to be dose related. There is no radiologic evidence that any of the drugs reduce fetal placental circulation. All these drugs cross the placenta in both directions.

Wilbanks GD, Campbell JA: Effect of *Herpesvirus hominis* Type 2 on human cervical epithelium: Scanning electron microscopic observations. *Amer J Obstet Gynec 112:924, 1972*

The clinical effects of *Herpesvirus hominis* Type 2 on the human cervix and vagina have been known for centuries. However, only recently has interest increased with the possible correlation of herpes infections with diseases of the fetus and neonate and cervical cancer. We have shown previously that the changes in the cells seen with herpes infection in Papanicolaou smears can be reproduced *in vitro*. Transmission electron microscopy shows only the presence of intra- and extra-cellular virus particles, but the scanning electron microscope reveals very striking and apparently unique changes in the cell surface following this infection. Scanning electron micrographs will be shown to illustrate these changes and to correlate them with the changes seen on cells in Papanicolaou smear preparations.

Orthopedics

Galante J, Rostoker W: Corrosion-related failures in metallic implants: An expreimental study. *Clin Orthop 86:237, 1972*

Four specimens each were prepared of the following materials with a special stresspoint design: Vitallium, 316L stainless steel, unalloyed titanium, Ti 6 percent Al 4 percent V, and Zircalloy. No evidence of stress-corrosion cracking was found in any specimen. Isolated pits were found on three specimens of Ti 6 percent Al 4 percent V, and in one of Vitallium and one of stainless steel. A titanium specimen showed light multiple pitting. The least tissue reaction was found around the Vitallium, stainless steel and unalloyed titanium coupons.

Radiology

Gose EE, Ackerman LV, Mucciardi AN, Alcorn FS: Computer diagnosis of breast cancer. *Proc Comput Image 1:731, 1972*

This research was carried out in two phases. In the first, properties of radiographs of the breast, or film mammograms (ordinary breast x-rays), were measured by a radiologist and the lesions were classified as benign or malignant by computer. In the second phase, properties of xeromammograms (xerographic breast x-rays) were measured by computer programs, which also rendered the classification. In both cases, the goal was to determine if a given lesion was benign or malignant, rather than to find the lesion initially.

In the first phase, it was shown that less than half the benign cases would have been operated upon (without missing any malignant cases) if the computer had made the decision, rather than the physician. In the second phase, it was shown that xerograms of lesions can be classified more accurately by computer than by expert radiologists.

Surgery

Southwick HW: Cancer of the tongue. *Surg Clin N Amer 53:147, 1973*

The management of tongue cancer by competent radiotherapy or surgery can produce reasonably satisfactory salvage rates for the mobile tongue when the lesion is T_1 or T_2. The larger lesions of the mobile tongue and posterior third and base of tongue have a much poorer prognosis. This area particularly requires imaginative joint treatment programs in an effort to improve the survival rate. Selective neck dissections are indicated.

Cardiovascular Surgery

Jensik RJ, Faber LP, Milloy FJ, Amato JJ: Sleeve lobectomy for carcinoma: A ten-year experience. *J Thorac Cardiovasc Surg 64:400, 1972*

1. Sleeve lobectomy resection for lung cancer was accomplished in 57 patients with an operative mortality rate of 1.8 per cent, an incidence of bronchial stenosis due to suture granulation of 7 per cent (four patients), and a local recurrence rate causing late stenosis of 7 per cent (four patients).
2. The survival rate for 54 patients undergoing sleeve lobectomy during the period from 1961 to 1971 was 30.3 per cent.
3. The use of preoperative irradiation increased the likelihood of sleeve resectability almost fourfold and resulted in no increase in complications.
4. An increased survival percentile for sleeve lobectomy is suggested when comparison is made with survival achieved by total lung resection.

Dye WS, Brown CM: Surgical correction of carotid and vertebral artery stenosis. *Surg Clin N Amer 53:241, 1973*

Surgery to relieve extracranial obstruction to cerebral flow has proved to be a valid treatment for cerebral vascular insufficiency. This is particularly true of isolated stenosis of carotid bifurcation producing transient ischemic attacks.

Najafi H, Dye WS, Javid H, Hunter JA, Goldin MD, Julian OC: Acute aortic regurgitation secondary to aortic dissection. Surgical management without valve replacement. *Ann Thorac Surg 14:474, 1972*

Emergency operations were performed in seven adult patients for severe aortic insufficiency caused by acute aortic dissection. Dissection beginning in the aortic root involved the entire thoracoabdominal aorta in at least three patients. The operative findings consisted of an arch of relatively normal caliber, supravalvular intimal tear, circumferential dissection, and prolapse of the aortic cups into the left ventricle. Repair of the proximal dissected layers and elevation of the cusps to their normal position restored valve competence in every patient. Six survivors have retained normal aortic valve function four months to six years postoperatively.

The review emphasizes the feasibility of restoring aortic valve competence without using a valve substitute in treating aortic insufficiency caused by acute aortic dissection.

Najafi H, Serry C, Dye WS, Javid H, Hunter JA, Goldin MD, Julian OC: Surgical management of complications of myocardial infarction. *Med Clin N Amer 57:205, 1973*

Although most patients suffering an initial myocardial infarction are able to resume relatively normal activities, a significant number are permanently incapacitated and in many instances death results from myocardial necrosis. Among the more lethal complications of myocardial infarction are rupture of the ventricular septum, disruption of the papillary muscle causing mitral insufficiency and ventricular aneurysm. Fortunately in the majority of instances these conditions lend themselves to successful surgical treatment. Early diagnosis, proper surgical indication, and appropriate operative procedure(s) are the cardinal prerequisites for this success and in part form the basis for this report.

SUGGESTIONS TO AUTHORS

Manuscripts. Manuscripts should be typewritten and double-spaced throughout, including tables, captions, references, etc. The title should be typed in all capitals and begin at the normal lefthand margin of Page 1, running across the entire page, with continuation on next line, if necessary, Authors' names should be listed in all capitals below title, one author per line, with double-spacing between names. In footnotes on Page 1, please identify departmental source of article and staff and academic ranks of all authors.

Abstract. A suitable summary, or abstract, should be prepared for each manuscript. This will precede the article. The abstract should contain all the conclusions of the article itself.

Figures should be drafted in black India Ink, with legends typed on a separate sheet in numerical order, using Arabic numbers corresponding to figures. Glossy photographs are preferred to original charts. Medical drawings may be submitted in the original or glossy prints. Photographs and Figures should be lightly identified on back, as to number and "Top," together with last name of author. Use Roman numerals to designate Tables, and include descriptive headings under numbers. Indicate in text where Figures and Tables occur.

Abbreviations preferred are: ml, kg, gm, mg, μg, mm, and mEq/l.

References. Number references serially in text, and list in numerical order, beginning on a new page, as follows:

1. Gary GW, Bryan AC, Frayser R, Houston CS, Rennie IDB: Control of acute mountain sickness. Aerospace Med 42:81, 1971

Abbreviations of journals should correspond to those in *Index Medicus.* List book references as follows:

2. Rafelson ME Jr, Brinkley SB, Hayashi JA: *Basic Biochemistry. Third Edition.* New York, Macmillan Company, 1971, pp. 96-208

Reprints. One hundred reprints with identifying cover are supplied free of charge for each article published. Additional reprints are supplied at cost.

IMMEDIATE PROGNOSIS IN THE MEDICAL INTENSIVE-CORONARY CARE UNIT: A REPORT OF 607 CONSECUTIVE PATIENTS

PHILIP R. LIEBSON

ABSTRACT. In the first nine months of the Presbyterian-St. Luke's Medical Intensive-Coronary Care Unit 607 patients were admitted. Total mortality in the Unit was 17.3 percent. Mortality for patients with myocardial infarction was 20.3 percent. Of those with cardiac arrest before or during admission to the Unit, 60.3 percent expired in the hospital. Eighteen patients died within 10 days of discharge from the Unit, and only two of these were unexpected deaths.

Of the 21 patients readmitted within 10 days of transfer from the Unit, 14 had an original diagnosis of myocardial infarction or angina and were re-admitted because of cardiac arrest, life-threatening arrhythmia, or further ischemia.

In conclusion, ultimate survival for any patient who developed cardiac arrest was poor; mortality for myocardial infarction was comparable to that of other coronary care units. A minority of patients with myocardial infarction, discharged from the Medical Intensive Care Unit with arrhythmias or conduction blocks, may benefit from admission to an intermediary care facility for a short period after discharge from the Unit.

INTRODUCTION

Presbyterian-St. Luke's Hospital inaugurated a Medical Intensive-Coronary Care Unit (MICU/CCU) in 1972. Its purpose was to decrease deaths from myocardial infarction through increased patient surveillance, and to reduce mortality in patients with serious medical disorders by intensive medical and nursing care. This is a report of the results of the effectiveness of the Unit during its first nine months.

From the Section of Cardio-Respiratory Diseases, Department of Medicine, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois

Philip R. Liebson, M.D., Assistant Attending Cardiologist, and Director, Medical Intensive-Coronary Care Unit, Presbyterian-St. Luke's Hospital; Assistant Professor of Medicine, Rush Medical College

DESCRIPTION OF THE MICU/CCU DESIGN AND EQUIPMENT:

A 16-bed MICU/CCU was constructed as an autonomous, self-sufficient unit in a wing of the medical service pavilion. The equipment includes hydraulic beds, central oxygen and suction outlets, multiple electrical outlets with appropriate grounding, a cardiac arrest alarm system, and 16 bedside units suitable for monitoring electrocardiagrams. Each bedside oscilloscope is connected to a central console in the nursing station, which consists of four banks of oscilloscopes and an alarm system sensitive to changes in heart rate. Individual electrocardiographic patterns of up to 16 patients are under constant surveillance simultaneously. Four defibrillators are available for use. Emergency drugs, equipment for cardiac pacemaking, ventilation, and a direct-writer

electrocardiograph are immediately available. The Unit is subdivided as follows: (1) an open three-bed area, (2) an open two-bed area, (3) five closed single-bed rooms, (4) three closed two-bed units. The five single rooms, farthest from the nursing station, have continuous television monitoring of the patients, with the monitors located at the nursing station.

The Nursing Staff

Each nurse has completed a training course, presented under the supervision of the cardiology and nursing divisions, prior to working in the Unit. The course emphasizes recognition and treatment of arrhythmias, heart failure and cardiac arrest. In addition, acid-base balance, respiratory management, and management of other intensive care problems such as neurologic, renal and gastrointestinal crises are taught. Continued education of the nursing staff is maintained by periodic review sessions and frequent analyses of experiences in the Unit. Nurses are taught to defibrillate patients under special situations.

Physicians

At least one member of the MICU/CCU house staff, which consists of two interns and two residents, is present in the Unit at all times, without exception. Daily rounds are made by the house officers under the direct supervision of the Unit's director, who is a member of the division of cardiology. The director is also available for consultation at other times. Each new group of house officers, rotating through the Unit monthly, receives special lectures and demonstrations on the recognition of arrhythmias, therapy of complications, myocardial infarction, and all aspects of cardiac resuscitation. In addition, subspecialists from other areas lecture in their fields. The attending physician of the patient in the MICU/CCU remains the physician of record. He attends the patient as he would on any other patient floor. However, only house officers are permitted to write orders. Complications are managed by the house officers and subspecialty consultants according to established therapeutic regimen, and routine management of all patients in the MICU/CCU is carried out by the medical house staff under supervision of the director of the Unit and attending physician. The director and house staff have ultimate responsibility for determining which patients should be admitted to the MICU/CCU.

Paramedical Personnel

Respiratory Therapist: At least one respiratory therapist, responsible to the respiratory division, is available at all times in the MICU/CCU. The therapist assists in respiratory care of the patient, performs blood gas determinations, and supervises the use of ventilatory-assist machines.

Chest Physiotherapist: At least one chest physiotherapist is available in the MICU/CCU during weekday hours to assist nurses and therapists in respiratory care including postural drainage, use of ultrasonic mists, vibration and percussion.

Diagnostic Classification

Patients are considered candidates for the Unit if they have the following illnesses or complications:

Group 1 (Cardiac Care Patients): Suspected or proven acute myocardial infarction; pre-infarction angina or unstable angina; life-threatening arrhythmias, and severe congestive heart failure.

Group 2 (Intensive Care Patients): Examples include potentially salvageable patients after cardiorespiratory arrest; patients with severe respiratory distress; complicated neurologic problems; all patients immediately following renal transplantation; patients with severe gastrointestinal hemorrhage.

The cardiac care patients, Group 1, are isolated in the closed bed areas, when possible, to allow for as much quiet as possible. The intensive care patients, Group 2, who need greater minute-to-minute nursing care, are kept in the open unit facilities, when possible.

Duration of Stay

Patients with possible myocardial infarction remain in the Unit at least three days, and electrocardiographic and enzyme activity are monitored to determine whether infarction has taken place. Those without definite infarction may be discharged in three days. Those with definite infarcts are kept in the Unit a minimum of six days, and longer if complications ensue. Criteria for diagnosis of acute myocardial infarction include a compatible clinical history of development of diagnostic Q waves, or evolution of ST segment and T wave abnormalities on electrocardiogram, with characteristic changes in creatine phosphokinase, serum glutamic-oxalacetic transaminase, serum glutamic-pyruvic transaminase, and lactic dehydrogenase.

Intensive care patients, Group 2, have a wide variety of disorders requiring fairly close nursing care. These patients are kept in the Unit until their condition stabilizes or it is felt that further intensive care could not affect eventual prognosis. For example, patients post-arrest who have had poor neurologic responsiveness and who show no evidence of recovery would be discharged from the Unit.

RESULTS

Diagnoses of Patients Admitted to MICU/CCU

Between September 1972 and June 30, 1973, a period of nine months, 607 patients were admitted to the Unit. This figure includes readmissions. Definitive diagnoses of these patients are listed in Table I. Over 60 percent were admitted for cardiac problems. Over 44 percent of those admitted for possible myocardial infarction had this diagnosis substantiated on the basis of enzyme and electrocardiographic studies. The most common non-cardiac diagnosis was respiratory disease, which accounted for 16 percent of patients admitted to the Unit. Mortality rate in the Unit was 17.3 percent (See Table II). Of those who survived, the vast majority were transferred to the regular medical service. Of the patients transferred to the surgical service, the usual reason was for emergency coronary bypass procedure and/or left ventricular aneurysmectomy. Other patients were transferred to the surgical service because of intractable gastrointestinal bleeding.

TABLE I

DIAGNOSIS OF 607 PATIENTS ADMITTED TO MICU/CCU

	TOTAL DIAGNOSED
TOTAL CARDIAC	430
Coronary artery disease	271
Definite myocardial infarction	118
Possible infarction	20
Angina and no infarction	133
Non-coronary heart disease including Arrhythmia	159
RESPIRATORY DISEASE	102
GASTROINTESTINAL—HEPATIC	35
NEUROLOGIC, INCLUDING OVERDOSE	30
CHRONIC RENAL DISEASE	19
METABOLIC	17
HEMATOLOGIC	8
GRAM NEGATIVE SEPSIS, WITH SHOCK	6
TOTAL	647*

*Total >607 because several patients had more than one primary problem.

TABLE II

ADMISSIONS TO MICU/CCU AND SURVIVAL

9/28/72 to 6/30/73

CLASSIFICATION	NO.
COMPLETED ADMISSIONS	607
Died in Unit	108 (17.3%)
TRANSFERRED	499
To surgical service	40
To medical service	459

Causes of Death in the MICU/CCU

The commonest cause of death was myocardial infarction, in 24 patients (See Table III). Patients who had been admitted to the Unit after a cardiac arrest without specific diagnostic classification constituted the second largest group. Patients admitted after a cerebrovascular accident who remained in coma constituted the third largest group.

TABLE III

CAUSES OF DEATHS IN MICU/CCU

CAUSE OF DEATH	NO.
Myocardial infarction	24
S/P cardiac arrest	22
Cerebral vascular accident—coma	14
Cirrhosis with coma or G.I. bleeding	8
S/P respiratory arrest	7
Chronic renal disease, including transplants	7
Chronic valvular heart disease	5
Other respiratory disease	5
Refractory arrhythmia	4
Miscellaneous	12
TOTAL	108

Slightly less than 70 percent of deaths in the Unit occurred within the first two days of admission (See Table IV). Almost 80 percent occurred within the first five days of admission, and over 95 percent within 10 days.

TABLE IV

MORTALITY IN MICU/CCU

Days From Unit Admission to Death		
DAYS	NO	Cumulative Percentage of All Deaths
0—2	73	68.2%
3—5	11	77.5%
6—10	20	96.4%
> 10	4	100.0%
TOTAL	108	

Of the 73 patients who died within two days of admission to the Unit, 15 were admitted after cardiac arrest with persistent coma, 13 died after documented myocardial infarction, and eight had cerebrovascular accidents with persistent coma. Other less common causes of death in this group were intractable arrhythmias without infarction, chronic valvular heart disease with end-stage failure, cirrhosis with gastrointestinal bleeding or hepatic coma, pulmonary embolus, septic shock, intestinal obstruction, myxedema coma, regional ileitis, carcinoma with metastases, end-stage renal failure, interstitial viral pneumonia, pneumococcal meningitis, pneumococcal pericarditis, and myeloproliferative syndrome with disseminated intravascular coagulation.

Of the 11 patients who died within three to five days after admission, three died of myocardial infarction with cardiogenic shock, and four remained comatose after previous cerebrovascular accident or cardiac arrest. Other causes of death included pulmonary emboli, chronic renal failure, and massive gastrointestinal hemorrhage. In summary, 34 of 84 patients who died within five days of admission entered the Unit in coma and never became responsive. Of all 108 deaths in the Unit, 45 were admitted in coma and never became responsive (41.7 percent).

Analysis of Possible Preventable Deaths In MICU/CCU

Review of all deaths in the Unit isolated nine cases of 108 who might possibly have survived, although all were in critical condition on admission to the Unit. Following are capsule summaries of the course of these nine patients.

Patient #1 (C.R.): Died one day after admission. Headache and myalgia; became comatose and was admitted to the MICU/CCU; had meningismus, seizures, temperature to 106 degrees. Antibiotics promptly started; pneumococci grown, spinal fluid obtained; patient became hypotensive. *Comment:* Although this was a fulminant infection, it is possible that pyrexia could have been better controlled.

Patient #2 (W.G.): Died within hours after admission. Admitted from another hospital; was in respiratory distress; possible viral interstitial pneumonia; six months pregnant; on prompt intubation; patient pulled out nasotracheal tube several hours later, but developed cardiac arrest and died. *Comment:* Attempt at reinsertion of tube was made promptly but difficult to accomplish. Cardiac arrest ensued and patient died. Severe interstitial pneumonia probably would have caused death, but difficulty in reinserting the nasotracheal tube could have initiated reflexes contributing to arrest.

Patient #3 (W.J.): Died one day after admission. Admitted in ketoacidosis after respiratory arrest with pancreatitis and possible gastritis; right femoral embolus occurred; removed surgically and returned to MICU/CCU; began to develop gangrene of right leg; packed in ice; marked hyperkalemia ensued (k+ = 7.9 mEq/1) despite packing of leg. Died of cardiac arrest despite marked efforts to decrease potassium concentration. *Comment:* Unlikely but possible that patient could have survived had leg been amputated.

Patient #4 (E.K.): Died seven days after admission to MICU/CCU. Admitted with chronic obstructive pulmonary disease; cor pulmonale, increased lethargy; ascites; on venti-mask and IPPB; on digitalis. Developed nodal rhythm and right bundle branch block; cardiac arrest one day after admission with hypokalemia; resuscitated; next day, hypercalcemic, hypertensive; intubated; placed on isoproterenol drip; renal failure and death ensued. *Comment:* More vigorous treatment of hypokalemia might have prevented arrest, which added to an already tenuous situation.

Patient #5 (D.M.): Died one day after admission. Metastatic bronchial carcinoma; calcium was 15 mEq/1; cardiac arrest despite attempts to lower calcium; not resuscitated. *Comment:* Extremely questionable whether this really was a preventable death, although marked hypercalcemia was a possible contributing cause.

Patient #6 (E.N.): Died 10 days after admission. Hodgkin's disease; pneumococcal meningitis; started promptly on penicillin and oxacillin; developed pneumococcal pneumonia, hypocalcemia, respiratory arrest; intubated; grand mal seizure; terminal pneumonia, and atelectasis. *Comment:* Another case of extremely questionable survival, even without the arrest situation; but awareness of hypocalcemia, though eventually treated, may have been delayed.

Patient #7 (A.M.): Died one day after admission. Spree alcoholic, admitted with pneumonia; developed tension pneumothorax, probably due to resuscitation after respiratory arrest. Bilateral chest tubes placed about six to eight hours after pneumothorax developed. Hypotension developed and the patient succumbed. *Comment:* We cannot gauge the contribution of pneumothorax to cause of death, but the chest condition may have occurred as a result of resuscitation attempts.

Patient #8 (B.T.): Died on day of admission to the Unit. Clear-cut signs of bowel obstruction. Surgical consultants called in. It was decided to temporize. Cantor tube inserted to decompress bowel. Potassium increased to 7.7 mEq/1; respiratory arrest followed; could not be resuscitated. Autopsy report showed emboli to mesenteric arteries and small bowel infarction. *Comment:* Early surgery possibly could have prevented death. Hyperkalemia uncontrolled another possible contributor to death.

Patient #9 (J.B.): Died on day of admission. Myxedema coma; hematocrit, 18; dehydrated; became bradyarrhythmic and hypotensive; L-thyroxine was started; respiratory arrest occurred; resuscitated; anuria; died. *Comment:* Could the possible availability of rapid-acting intravenous thyroid preparations like L-truodothyromine have prevented death?

Deaths After Transfer From MICU/CCU

Approximately seven to eight percent of the patients transferred from the Unit died within 30 days of transfer (See Table V). Twenty-five percent of patients admitted to the surgical service died within this period, and 6.1 percent of

TABLE V

DEATHS WITHIN 30 DAYS OF TRANSFER FROM MICU/CCU

	NO.	DIED
TOTAL TRANSFERRED FROM UNIT	499	38 (7.6%)
To surgical service	40	10 (25.0%)
To medical service	459	28 (6.1%)

patients admitted to the medical service succumbed. Most surgical deaths were in patients with severe coronary artery disease who had had bypass procedures, or those with severe gastrointestinal bleeding who had required surgical intervention in order to stop the hemorrhage.

Of the 28 patients who died within 30 days of transfer from the MICU/CCU to the general medical service, 18 died within 10 days (See Table VI). Analysis of all deaths within 30 days of transfer to the medical service (Table VII) shows that the most common diagnosis at the time of transfer was coma after cardiorespiratory arrest, eventually accounting for 50 percent of deaths. Five patients died who had been discharged from the Unit after myocardial infarction, and five died with chronic respiratory disease. One death was attributed to each of the following: chronic valvular heart disease, acute valvular heart disease with endocarditis and pneumonia, leukemia, and coagulation defect in a post-renal transplant patient.

Table VIII lists the condition of patients transferred from the MICU/CCU to the medical service who died within 10 days of transfer. Only two of the 18 patients in this group died unexpectedly. Of the two unexpected deaths, one patient (E.M.) had had chest pain for two days, beginning seven days after transfer from the MICU/CCU. This suggested a new ischemic event, although electrocardiograms were unchanged. Cardiac arrest then ensued, with no response to efforts at resuscitation. The patient who died after infectious endocarditis (D.F.) was found dead in bed the day following transfer from the Unit. He had just been weaned off a respirator. He might have been resuscitated had he been in a more centrally located bed after discharge from the Unit. Of the other 16 expected deaths within 10 days of transfer from the Unit, eight patients had remained continuously in coma and eight were considered moribund on transfer.

TABLE VI

DEATHS WITHIN 30 DAYS OF TRANSFER FROM MICU/CCU TO MEDICAL SERVICE

TIME FROM TRANSFER TO DEATH (DAYS)	NO.
0— 9	18
10—19	5
20—29	5
TOTAL	28

TABLE VII

CAUSE OF DEATHS WITHIN 30 DAYS OF TRANSFER FROM MICU/CCU TO MEDICAL SERVICE

CAUSE OF DEATH	NO.
Neurological dysfunction after cardiorespiratory arrest (coma)	14
Post-myocardial infarction	5
Chronic respiratory disease	5
Chronic valvular heart disease	1
Acute valvular heart disease: endocarditis + pneumonia	1
Leukemia	1
Renal transplant—coagulation defect	1
TOTAL	28

Analysis of Patients With Cardiopulmonary Arrest

This group includes those with unexpected respiratory arrest, ventricular asystole, sustained ventricular tachycardia requiring electrical cardioversion, or ventricular fibrillation. A total of 106 patients experienced cardiopulmonary arrest either before or during their MICU/CCU stay (Table IX). Over 60 percent of patients with cardiopulmonary arrest died in the hospital. Of those admitted to the MICU/CCU *after* cardiopulmonary arrest, slightly over 50 percent died in the hospital, most of them in the Unit. Of those patients who sustained their first cardiopulmonary arrest after admission to the Unit, 87.6 percent died in the hospital, all in the Unit. Only nine patients developed cardiopulmonary arrest both before and during MICU/CCU admission. Of these, 44.4 percent died in the hospital. This latter group predominantly included patients with refractory arrhyth-

TABLE VIII

ANALYSIS OF DEATHS WITHIN 10 DAYS OF TRANSFER FROM MICU/CCU TO MEDICAL SERVICE

PATIENT	AGE	DAYS POST-TRANSFER	CONDITION ON TRANSFER FROM MICU/CCU
J.D.	75	9	Cerebral vascular accident plus shock lung
C.O.	82	2	Coma after cardiac arrest
F.S.	82	2	Massive pulmonary embolus
C.S.	65	6	Respiratory arrest plus coma
E.G.	55	3	Cerebral vascular accident plus respiratory insufficiency
E.W.	70	1	Cirrhosis with hepatic coma
E.M.	57	9	S/P infarction—right bundle branch block*
T.M.	85	7	Cerebral vascular accident—coma
D.F.	41	1	S/P endocarditis*
E.S.	70	6	Coma after cardiac arrest
L.G.	45	1	Renal transplant plus cardiac arrest
H.B.	65	5	Coma after cardiac arrest
P.A.	81	3	S/P cardiac arrest after myocardial infarct
F.B.	58	8	Coma plus pneumonia
G.G.	43	3	Pneumonia plus alpha-antitrypsin deficiency
C.T.	83	<1	S/P cardiac arrest—ventricular tachycardia
F.G.	83	2	Coma after cardiac arrest
A.S.	81	4	Coma after respiratory arrest

*Unexpected death (See text)

TABLE IX

FATE OF PATIENTS WITH CARDIOPULMONARY ARREST

TIME OF ARREST	NO.	DIED IN UNIT	DIED AFTER TRANSFER	TOTAL DEATHS
Before admission to MICU/CCU	65	27	6	33 (50.6%)
Only in MICU/CCU	32	28	—	28 (87.6%)
Before and during stay in MICU/CCU	9	3	1	4 (44.4%)
TOTAL	106	58	7	65 (61.3%)

mias requiring frequent electrical cardioversion for ventricular tachycardia or fibrillation.

Analysis of Course of Patients With Cardiopulmonary Arrest Before Admission to MICU/CCU Only

In 65 patients who were admitted to the MICU/CCU because of cardiopulmonary arrest the most common admitting diagnoses (15 patients) were chronic pulmonary disease, pneumonia, or pulmonary embolus (see Table X). The second most common diagnosis was acute myocardial infarction (13 patients); the third, chronic non-coronary heart disease (8 patients). A little over 50 percent of patients who had cardiopulmonary arrest before admission to the Unit died in the hospital. Mortality rate was higher for those patients who had not sustained an acute myocardial infarcation than for those who had developed cardiopulmonary arrest in conjunction with an acute myocardial infarction. Of those sustaining cardiopulmonary arrest with acute myocardial infarction, 38.4 percent died in the hospital. Of the seven patients who had evidence of coronary artery disease without recent infarct, who had sustained

TABLE X

ANALYSIS OF COURSE OF PATIENTS WITH CARDIOPULMONARY ARREST BEFORE ADMISSION TO MICU/CCU

ADMITTING DIAGNOSIS	NO.	DIED IN UNIT	DIED AFTER TRANSFER	TOTAL DEATHS
Chronic pulmonary disease, pneumonia, pulmonary embolus	15	6	2	8 (53.4%)
Acute myocardial infarction	13	3	2	5 (38.4%)
Chronic heart disease	8	5		5 (62.5%)
Coronary artery disease without recent infarct	7			
During or following surgical procedure	5	3	1	4 (80%)
Miscellaneous	17	10	1	11 (64.8%)
TOTAL	65	27	6	33 (50.6%)

cardiopulmonary arrest before admission to the Unit, every patient left the hospital. Over 50 percent of patients with chronic pulmonary disease who had sustained a cardiopulmonary arrest before entering the Unit died in the hospital. Over 60 percent of the patients with chronic non-coronary artery disease and miscellaneous conditions who sustained cardiopulmonary arrest before admission to the Unit died in the hospital.

Analysis of Patients With Cardiopulmonary Arrest In MICU/CCU Only

Mortality of patients who sustained cardiopulmonary arrest only after admission to the MICU/CCU was quite high. Of these patients, 87.6 percent died in the Unit (Table XI). The most common single cause of cardiopulmonary arrest in the Unit was acute or impending myocardial infarction. Thirteen of these patients sustained cardiopulmonary arrest in the Unit, 10 of whom died in the Unit (77 percent). Mortality figures were higher for those without acute myocardial infarction who sustained cardiopulmonary arrest in the Unit. Of these patients, 94.6 percent died in the Unit, although some had been previously successfully resuscitated.

Fate of Patients With Ventricular Tachycardia Converted Spontaneously or Pharmacologically (Unsustained Ventricular Tachycardia)

Prognosis for patients with ventricular tachycardia who did not need electrical cardioversion (unsustained or responsive ventricular tachycardia) was much better than for the cardiac arrest group (See Table XII). Most of the patients had coronary artery disease, 40 percent having myocardial infarction. Of all patients with ventricular tachycardia converting spontaneously or pharmacologically, whether before admission to the MICU/CCU or only in the MICU/CCU, 16 percent died in the hospital. No patient who developed responsive ventricular tachycardia before admission to the MICU/CCU died in the hospital. Four of 13 patients who developed responsive ventricular tachycardia in the MICU/CCU, who converted spontaneously or pharmacologically, died in the hospital (30.9 percent).

Prognosis After Myocardial Infarction With Cardiopulmonary Arrest or Unsustained Ventricular Tachycardia

Of 27 patients with documented myocardial infarction who had experienced cardiopulmonary arrest before admission

or in the MICU/CCU, 55.6 percent died in the hospital (Table XIII), most of them in the Unit. Of the patients who sustained cardiac arrest before admission to the MICU/CCU, 38.4 percent died in the hospital. Of the patients who developed arrest in the MICU/CCU only, 77 percent died while still in the MICU/CCU. Most cardiac arrests in the Unit were associated with congestive heart failure or cardiogenic shock.

There were 10 patients with myocardial infarction who developed unsustained ventricular tachycardia, converting spontaneously or with xylocaine: two before admission to the Unit, and eight in the Unit. None of these 10 patients died in the hospital.

TABLE XI

ANALYSIS OF PATIENTS WITH CARDIOPULMONARY ARREST IN MICU/CCU ONLY

DIAGNOSIS	NO.	DIED IN UNIT*
Pulmonary disease	8	8
Acute myocardial infarction—primary ventricular fibrillation	6	4
Acute myocardial infarction—cardiogenic shock	5	5
Possible myocardial infarction, coronary artery disease and congestive heart failure	2	1
Renal transplant	3	3
Endocrine or metabolic disorder	3	3
Gastrointestinal disease	2	2
Neurologic disease	2	1
Chronic heart disease—refractory congestive heart failure	1	1
TOTAL	32	28 (87.6%)
Myocardial infarct	13	10 (77%)
Other	19	18 (94.6%)

*None of the patients died within 30 days after transfer from Unit.

TABLE XII

FATE OF PATIENTS WITH VENTRICULAR TACHYCARDIA CONVERTED SPONTANEOUSLY OR PHARMACOLOGICALLY

TIME OF EVENT	NO.	DIED IN UNIT	DIED AFTER TRANSFER	TOTAL DEATHS
Before admission to MICU/CCU	10	—	—	—
Only in MICU/CCU	13	2	2	4 (30.9%)
Before and during stay in MICU/CCU	2	—	—	—
TOTAL	25	2	2	4 (16%)

TABLE XIII

FATE OF PATIENTS WITH MYOCARDIAL INFARCTION AND CARDIOPULMONARY ARREST

TIME OF ARREST	NO.	DIED IN UNIT	DIED AFTER TRANSFER	TOTAL DEATHS
Before admission to MICU/CCU	13	3	2	5 (38.4%)
Only In MICU/CCU	13	10	—	10 (77%)
Before and during stay in MICU/CCU	1	—	—	—
TOTAL	27	13	2	15 (55.6%)

Readmissions to the MICU/CCU

Of the 618* patients admitted to the Unit, 59 were readmissions (9.6 percent) (Table XIV). Of the 59 readmissions, 24 were readmitted within 10 days of initial transfer, 16 readmitted from 10 to 19 days of initial transfer, 7 readmitted from 20 to 29 days of initial transfer, and 12 readmitted 30 or more days from initial transfer. The last group consisted predominantly of those who were discharged from the hospital before readmission to the Unit. We analyzed the readmissions on the basis of original diagnosis and reasons for readmission to the MICU/CCU.

TABLE XIV

READMISSIONS TO MICU/CCU

	NO.
TOTAL INITIAL ADMISSIONS	559
TOTAL READMISSIONS	59
Time From initial transfer	
0— 9 Days	24
10—19 Days	16
20—29 Days	7
30 + Days	12

Patients Readmitted to the MICU/CCU Within 20 Days After Unit Transfer

Patients readmitted within 10 days of transfer from the MICU/CCU most commonly had been admitted to the Unit originally because of myocardial infarction (See Table XV). Other diagnoses included angina, arrhythmia with organic heart disease, renal transplant, chronic renal disease, bacterial endocarditis, and pneumonia. Of those readmitted 10 to 20 days after initial transfer from the Unit, original diagnosis had been arrhythmia with organic heart disease in four of the patients. In this 10-to-20-day group, three patients originally had sustained myocardial infarction, two had suffered respiratory insufficiency, two had had angina, one had developed complications from valvular heart disease, and one had sustained pulmonary embolus.

Reasons For Readmission of Patients to MICU/CCU Within 20 Days of Initial Transfer From Unit

The vast majority of those transferred back within 10 days after leaving the Unit were returned because of cardiac problems (See Table XVI). Five had life-threatening arrhythmia; six had cardiac arrest; four had myocardial ischemia; two had myocardial infarction; one was readmitted because of a hypertensive episode; and one was readmitted because of pneumonia after valve surgery.

Of the non-cardiac causes, one patient was transferred back to the Unit because of respiratory arrest, three because of post-renal transplant complications, and one because of coagulopathy associated with chronic renal disease.

Of those readmitted to the Unit 10 to 20 days after initial admission, readmitting diagnosis was of cardiac nature in 13 of 16. Life-threatening arrhythmia associated with organic heart disease was the most common readmission diagnosis in this group of patients. Only two of these readmissions were occasioned by cardiac arrest, compared with six in the early readmission group. The development of an ischemic episode or infarction was a relatively uncommon cause for readmission to the Unit in the latter group. Thus, most of the possible reinfarctions occurred within 10 days of transfer from the Unit.

Those requiring readmission, therefore, frequently had developed marked arrhythmias during their original stay in the Unit.

DISCUSSION

Rationale For MICU/CCU

The Medical Intensive-Coronary Care facility was opened to (1) decrease mortality and morbidity; (2) provide for an intensive area of teaching for physicians

*Includes 11 patients who were still in the Unit on June 30, 1973.

TABLE XV

ORIGINAL DIAGNOSIS OF PATIENTS READMITTED TO MICU/CCU WITHIN 20 DAYS AFTER TRANSFER FROM UNIT

0-9 DAYS	NO.	10-20 DAYS	NO.
Myocardial infarction	11	Arrhythmia, organic heart disease	4
Angina	3	Myocardial infarction	3
Arrhythmia, organic heart disease	3	Respiratory insufficiency	2
Renal transplant	1	Angina	2
Chronic renal disease	1	Valvular heart disease	1
Bacterial endocarditis	1	Pulmonary embolus	1
Pneumonia	1		
TOTAL	21	TOTAL	13

TABLE XVI

REASONS FOR READMISSION OF PATIENTS TO MICU/CCU WITHIN 20 DAYS OF ORIGINAL TRANSFER FROM UNIT

0-9 DAYS	NO.	10-20 DAYS	NO.
TOTAL CARDIAC	19	TOTAL CARDIAC	13
Life-threatening arrhythmia	5	Arrhythmia, organic heart disease	9
Cardiac arrest	4	Cardiac arrest	1
Myocardial ischemia	4	Myocardial ischemia	1
Myocardial infarction	2	Arrhythmia, post-coronary bypass	1
Hypotensive episode, post-coronary angio	1	Cardiac arrest, post-coronary bypass	1
Cardiac arrest, angina	1	RESPIRATORY ARREST	3
Cardiac arrest, S/P pneumonia	1		
Pneumonia, S/P valve surgery	1		
RESPIRATORY ARREST	1		
POST-RENAL TRANSPLANT COMPLICATIONS	3		
COAGULOPATHY, CHRONIC RENAL DISEASE	1		
TOTAL	24*	TOTAL	16*

*Several patients were readmitted more than once.

and paramedical staff; (3) develop techniques of clinical evaluation. This report is an analysis of the effectiveness of the Unit in decreasing mortality during the first nine months of its existence. In order to discuss this question on the basis of our results, we must divide the results into (1) those concerning a homogeneous group of patients—those with acute myocardial infarction, and (2) a heterogeneous group—those with severe medical disorders requiring general medical intensive care.

Mortality Following Myocardial Infarction

Vast literature has developed over the past decade which indicates that between 60 and 95 percent of patients with myocardial infarction experience an arrhythmia within the first 72 hours after an infarct.[1-3] Approximately 10 percent of myocardial infarction patients suddenly develop ventricular fibrillation.[4] The frequency of arrhythmias, including ventricular fibrillation, progressively decreases after approximately 72 hours. Many studies indicate that approximately half of expected in-hospital mortality of patients with myocardial infarction is due to sudden arrhythmia in the absence of other life-threatening limitations of cardiac function.[5,6] Before the development of cardiac care units, in-hospital mortality from infarction was approximately 30 to 40 percent.[7] The development of cardiac

care units has decreased mortality to between 15 and 20 percent.[8] This has been accomplished primarily by prevention and treatment of life-threatening arrhythmias. Our mortality rate of 20.3 percent is comparable to that experienced in other coronary care facilities. As in other facilities, the decrease in mortality from the expected 30 to 40 percent has been due primarily to prevention and treatment of life-threatening arrhythmias.

The primary cause of mortality in the Coronary Care Unit, in patients with myocardial infarction, is the development of cardiogenic shock. Recent studies have indicated that cardiogenic shock results in mortality rate between 70 and 95 percent, despite the use of inotropic agents such as levarterenol, isoproterenol, dopamine, and glucagon.[9-11] More recent studies with intra-aortic balloon counterpulsation suggest that in many patients the cardiogenic shock condition may be reversed temporarily, but overall mortality figures have not improved markedly with the use of intra-aortic balloon counterpulsation alone.[12,13] Our treatment of patients with cardiogenic shock after myocardial infarction has been limited thus far to the use of cardiac inotropic drugs, with no difference from the dismal mortality figures at other centers using these agents alone.

Initiation of resuscitation of patients with cardiac arrest in the Unit with myocardial infarction has been rapid, usually beginning within 30 seconds of arrest. We have found, however, that the in-hospital mortality of patients who have sustained a cardiopulmonary arrest, in the MICU/CCU after myocardial infarction has been 77 percent. Most of these patients have had associated cardiogenic shock. In several studies, it has been shown that successful resuscitation from cardiopulmonary arrest in situations with acute myocardial infarction ranges from 14 to 75 percent.[7] In a review of another large group of patients sustaining cardiac arrest with acute myocardial infarction, only 7.2 percent were discharged from the hospital alive.[14]

In our overall group of patients with myocardial infarctions and cardiopulmonary arrest either before admission or during stay in the Unit, we found that 45 percent were eventually discharged from the hospital. Although this figure compares well with the average from other centers, it must be stressed that patient group, age group, the severity of infarct, and the speed with which a patient is hospitalized might affect mortality figure comparisons. For example, patients with acute myocardial infarction who died from cardiac arrest in the hospital emergency room, before they could be brought to the Unit, were not included in our mortality figures.

Intensive Care Unit Patients

Intensive-care patients constitute a heterogeneous group, and it is difficult to compare mortality rates in one heterogeneous group with those in another. Mortality figures have been quite high in patients with intensive care problems who have developed cardiac arrest.[14,15] Almost 95 percent of patients who developed cardiopulmonary arrest with intensive care unit problems while in the Unit did not survive hospitalization, and those admitted to the Unit after cardiopulmonary arrest had mortality of slightly over 50 percent. Other studies have shown an equally ominous prognosis in patients developing cardiac arrest outside a surgical facility. Camarata, *et al.* show long-term survival of five percent in a group of patients sustaining cardiac arrest.[15] Stemmler found that only 8.8 percent of a large series of patients sustaining cardiac arrest outside the operating room had been discharged alive from the hospital.[14] Our results and the results of others suggest that the development of cardiac arrest in patients with intensive medical problems, whether or not the patient has an acute myocardial infarction, is an ominous sign, and perhaps may be seen as the result of life-threatening medical problems which have not responded to therapy. Success or failure in

a given attempt at resuscitation is unpredictable regardless of the severity of the predisposing illness, and therefore resuscitation should be started in each case.

Prevention of Life-Threatening Arrhythmias After Myocardial Infarction

Cardiac arrest in early acute myocardial infarction, perhaps within the first hour or two, is due primarily to ventricular fibrillation without underlying complications, and when treated promptly may produce a low mortality. This is the situation seen in mobile coronary care units where the patient is followed quite early from the time of his acute coronary event. Patients sustaining cardiac arrest in coronary care units, usually within eight hours after the acute coronary event, are more vulnerable to death from cardiac arrest, primarily because arrest later in the infarct period is more likely associated with complications such as congestive heart failure and myocardial infarction shock.[5] It is impossible to say how often cardiac arrest is prevented in our Unit because of prophylactic treatment with xylocaine whenever frequent ventricular extrasystoles are noted. We have initiated xylocaine therapy under the following circumstances: (1) the development of three or more ventricular extrasystoles in a row, (2) development of five or more unifocal ventricular extrasystoles per minute, (3) one or more series of multifocal ventricular extrasystoles, (4) the development of a QRS complex on a previous T wave. Any of these configurations of extrasystoles might presage the development of ventricular fibrillation.[16,17]

Approximately 70 percent of patients with documented myocardial infarction in our Unit were given xylocaine for ventricular arrhythmias. If we assume the mortality in non-coronary care facilities to average 30 to 40 percent in infarct patients, our mortality figure of 20.3 percent for myocardial infarction indicates that treatment of possible life-threatening arrhythmias before arrest decreases mortality in this group of patients.

Analysis of Deaths after Transfer from MICU/CCU

Of patients admitted to the Unit, there were only two unexpected deaths within the first 10 days after transfer to the general medical facility. This suggests that, except for those whose illness is of such severity that further intensive treatment is considered to be of no value, patients are generally stable when transferred. The intensive-care patient is usually kept in the Unit until his condition is stable. This includes good respiratory control, fluid and electrolyte balance, absence of arrhythmias, and a stable renal function. Patients with myocardial infarction remain in the Unit for a period of five to six days—longer if complications ensue.

It is difficult to predict which patients after myocardial infarction will develop reinfarction or further arrhythmias requiring closer observation. Our studies show that of patients *readmitted* to the Unit within a short period of time, the majority originally had sustained a myocardial infarction. Readmission of this group was due mostly to the development of life-threatening arrhythmia or recurrent chest pain. The possibility of an intermediary care or stepdown unit for patients with myocardial infarction should be considered, therefore, in special instances such as patients with frequent extrasystoles or evidence of persistent heart block.

In summary, our results show that establishment of the Medical Intensive-Coronary Care Unit has resulted in decreased mortality figures for myocardial infarction comparable to those of other coronary care facilities. The percent of patients discharged from the hospital after cardiac arrest, however, was quite low, as in other centers. Few patients, in

either the myocardial infarction or intensive-care group, died unexpectedly within 10 days of transfer from the Unit. A minority of patients after myocardial infarction had to be readmitted to the Unit within a short period of time because of extrasystoles or chest pain. These patients constituted the majority of patients readmitted to the Unit within the first 10 days after transfer.

ACKNOWLEDGEMENTS

I wish to thank Dr. T. B. Schwartz for his careful evaluation of the manuscript and his helpful comments.

I am indebted to Mrs. Shirley Williams for her excellent secretarial assistance.

REFERENCES

1. DeSanctis RW, Block P, Hutter AM Jr: Tachyarrhythmias in myocardial infarction. Circulation **45**:681, 1972
2. Killip T III, Kimball JT: Treatment of myocardial infarction in a coronary care unit: a two year experience with 250 patients. Amer J Cardiol **20**:457, 1967
3. Yu PN: Pre-hospital care of acute myocardial infarction. Circulation **45**:189, 1972
4. Restieaux N, Bray C, Bullard H, et al: One hundred, fifty patients with cardiac infarction treated in a coronary care unit. Lancet **1**:1285, 1967
5. Kimball JT, Killip T: Aggressive treatment of arrhythmias in acute myocardial infarction: procedures and results. Prog Cardiovas Dis **10**:483, 1968
6. Meltzer LE, Kitchell JB: The incidence of arrhythmias associated with acute myocardial infarction. Prog Cardiovas Dis **9**:50, 1966
7. Killip T, Kimball JT: A survey of the coronary care unit: concept and results. Prog Cardiovas Dis **11**:45, 1968
8. Marshall RM, Blount SG Jr, Genton E: Acute myocardial infarction: influence of a coronary care unit. Arch Int Med **122**:472, 1968
9. Scheidt S, Ascheim R, Killip T III: Shock after acute myocardial infarction: a clinical and hemodynamic profile. Amer J Cardiol **26**:556, 1970
10. Loeb HS, Winslow EBJ, Rahimtoola SH et al: Acute hemodynamic effects of dopamine in patients with shock. Circulation **44**:163, 1971
11. Lvoff R, Wilcken DEL: Glucagon in heart failure and in cardiogenic shock: experience in 50 patients. Circulation **45**:534, 1972
12. Scheidt S, Wilner G, Mueller H, et al: Intra-aortic balloon counterpulsation in cardiogenic shock: a report of a cooperative clinical trial. New Eng J Med **288**:979, 1973
13. Mueller H, Ayers SM, Gianelli S Jr, et al: Effect of isoproterenol, 1-norepinephrine, and intra-aortic counterpulsation on hemodynamics and myocardial metabolism in shock following acute myocardial inarction. Circulation **45**:335, 1972
14. Stemmler EJ: Cardiac resuscitation: a one-year study of patients resuscitated within a university hospital. Ann Int Med **63**:613, 1965
15. Camarata SJ, Weil MH, Hanashiro PK, Shubin H: Cardiac arrest in the critically ill: I. A study of predisposing causes in 132 patients. Circulation **44**:688, 1971
16. Epstein SE, Beiser GD, Rosing DR, et al: Experimental acute myocardial infarction. Circulation **47**:446, 1973
17. Lown B, Klein MB, Hershberg PI: Coronary and pre-coronary care. Amer J Med **46**:705, 1969

TRANSCUTANEOUS STIMULATORS IN PAIN CONTROL

Max S. Sadove
Richard D. Thomason

ABSTRACT. The use of electrical body surface stimulators for the relief of pain is presented with a discussion of the "gate" theory of Melzak and Wall which explains the apparent effectiveness of this device. Specific types of pain problems are discussed with expected relief in each case using the electrical stimulator alone or in conjunction with other treatment. The specifications of the equipment used are explained and the electrical output characteristics are shown in line drawings. Method of application of the electrodes and placement of electrodes for various pain problems is discussed for each category.

INTRODUCTION

Electrical body surface stimulators have been used for many decades by many individuals, especially by chiropractors, osteopaths and others. Physicians recently were made aware of this modality again when the dorsal column stimulator popularized by Norman Shealy was applied to body surfaces.[1-5] Many investigators have been wrapping nerves for interruption of pain syndromes. These were of interest to us, but not to a great degree until we realized that the current applied was not too different from that which we used in our electrical acupuncture and "electrical acupuncture anesthesia." In acupuncture we saw relief of facial pain and tic douloureux; we then reasoned that perhaps electrical skin stimulation of these areas through a skin pad would be effective also. A series of patients was then treated with the Transcutaneous Stimulator (TCS), and a high incidence of pain relief was obtained. Thereafter this modality became an integral part of our pain center's approach to therapy.

Initially we effectively used the Medtronic device which has two controls—rate and amplitude. It is neat and compact and has disposable electrodes. However on analysis we were curious about its electrical characteristics and we analyzed the output. We found that the output changed markedly in all parameters with changes in the load and amplitude as well as frequency settings. We therefore ordered several units made to our specifications by Theratron Corporation,* resulting in a device, called the Tran-Q-Lator, which had independent pulse rate settings, pulse duration settings, and pulse amplitude settings (Fig. 1). On this unit the frequency (pulsing rate) can be adjusted from 10 to 160 hz, the pulse width from 50 to 300 microseconds, and the voltage from 0 to 80 volts with a 500-ohm load. We have made various

From the Department of Anesthesiology, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois

Max S. Sadove, M.D., Chairman, Department of Anesthesiology, Rush-Presbyterian-St. Luke's Medical Center; Professor of Anesthesiology, Rush Medical College

Richard D. Thomason, M.D., Associate Attending Anesthesiologist, Presbyterian-St. Luke's Hospital; Assistant Professor, Rush Medical College

*Theratron Corporation, 2300 Foster Avenue, Wheeling, Illinois 60090

Fig. 1—The Tran-Q-Lator.

and sundry types, shapes and sizes of electrodes for special applications. The output is nearly a square-wave in character (Fig. 2).

Theoretical Consideration

In recent years the Melzak and Wall theory[6] has been widely discussed and acclaimed. In fact there are now proponents of a second gate higher in the CNS at the base of the brain especially attractive to those who use "acupuncture anesthesia" or, more correctly, "acupuncture analgesia."

The essence of the theory is that at the substantia gelatinosa there is a functional gate. This gate, or threshold modulator, is increased or decreased in its function by stimuli coming from the periphery via the somatic and/or visceral afferent fibers. Thus, rubbing or massage of a trigger area may relieve pain by raising the threshold. A stream of neural stimuli flowing from the periphery, whether or not they are continuous, intermittent, or pulsed and whether induced by a needle, a counter-irritant stimulus or a repetitive volley as from a Transcutaneous Stimulator, all have the potentiality of altering the gate and thus the awareness of pain. Internal neurocellular electrodes will have to be placed in living animals, possibly including man, to clarify finally exactly what is occurring. It may have an effect entirely different from that of the dorsal column stimulator. There can be no doubt that TCS has a real effect on the perception of pain. Also there is the very real probability that it may do more than simply act at the substantia gelatinosa; it may produce axon reflex activity or reflex activity of a visceral or somatic nature.

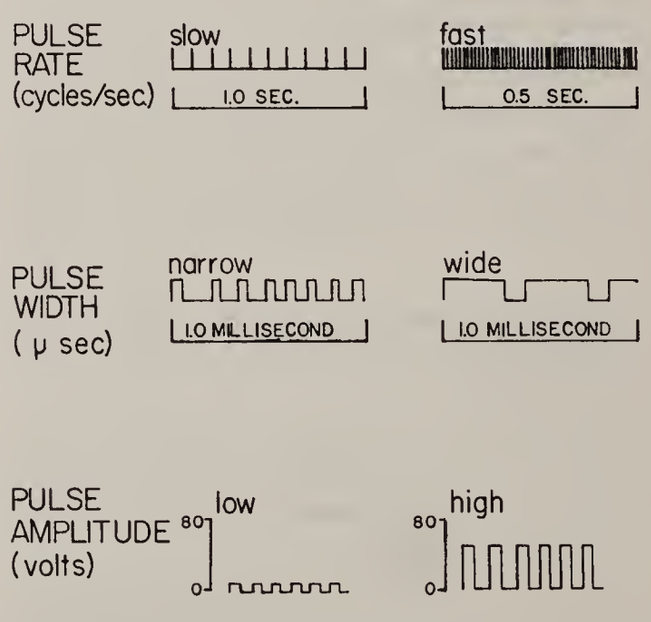


Fig. 2—Characteristics of the transcutaneous stimulator unit.

THERAPEUTIC CONSIDERATIONS

Application to type of pain problems seen in our pain center.

A. Tic Douloureux—Approximately three dozen patients have been treated with this unit. It definitely can be used to alter the pain of this condition. We see no evidence of curative value; that is, while the attacks do tend to lessen slightly in intensity and duration, they do not stop completely. However in several instances, dosages of drugs like Tegretol® have been coincidentally reduced with the same control of the syndrome. When the attacks start, the active electrode is placed over the area of maximal pain. In a matter of 10 to 15 minutes the area of pain decreases and is of less intensity. The severe pain in such areas as teeth, lip, nose, etc. lessens and gradually disappears. By 20 to 25 minutes in most instances the major portion of the pain has gone, leaving an area of some soreness. In some instances the unit can precipitate an attack, especially if the amplitude is increased too rapidly. Muscle-twitching may occur at various frequencies, but by increasing or decreasing the frequency or moving the active or ground electrode this annoyance may be eliminated. The amplitude may be adjusted until it is almost uncomfortable and then decreased to a comfortable level. One notices that with time adaption occurs, pain lessens, and so does the sensitivity to the electrodes. Thus amplitude must be adjusted upwards at intervals. The amplitude should be decreased slowly and the unit turned off before removal. In some patients who have used the unit in excess of 6 to 8 hours there has been some erythema of short duration, in the area of the electrodes. We have never seen actual skin injury but we warn the patient about output levels in areas that are hypoesthetic.

One might ask concerning the duration of relief. It can be as short as a few minutes after treatment, to as long as several days. There is no way we can predict. Many have subsequently been controlled by drugs such as Tegretol which previously had failed to control the attacks. At times we have also combined the TCS therapy with acupuncture and/or blocks with long acting local anesthetic solutions.

B. Neuritis—We have treated a number of various disease states loosely called "neuritis." These are pain syndromes in which the distribution of pain follows a "nerve" pattern, in which the pain is sharp-localized-piercing in nature and frequently is associated with sensory change as well as motor changes. Many syndromes have known etiologies and many do not. Many patients have intermittent attacks of pain mixed with milder pain, and frequently there is tingling or "pins and needles." If one places the active electrode in the area of the radiated pain and gradually increases the amplitude of the stimulator output, the pain will frequently subside in approximately 25 minutes. The psychic effect of stopping the pain is almost impossible to evaluate. Some patients have gone into a panic-like state when the instrument has been removed and is not available for the next attack.

It is poor medicine, or so we have been taught, to treat a symptom. But in many instances, after extensive evaluation, all that can be said is "it is a neuritis, a radiculitis, or possibly of osteoarthritic origin." It would be unwise to discontinue the search for a cause to treat only specifically but in many instances we have had little choice but to treat the symptoms. Blocking therapeutically with local anesthetics and even phenol or alcohol have not been logical or have failed, and narcotics were our only alternative. Repetitive evaluation during the course of pain control therapy is essential.

In some instances the best results have occurred by placing the active electrode and the indifferent electrode over the origin of the nerve roots involved or immediately paravertebrally. This electrode placement can be alternated with the

area of radiated pain. The patient quickly learns the best placement. Also in some instances it has taken as long as two hours to get adequate relief, as individual variation is great.

C. Phantom Pain—We have had several patients who have had phantom perineal pain of a causalgic type after abdominoperineal resection of the colon. We have also had some patients who have had the usual phantom limb pain. Applying the unit as close as possible to the area of maximal pain has resulted in loss of pain for variable periods of time. In several instances, after several applications the pain has disappeared for varying periods of time, similarly to that observed after sympathetic blocks. In several instances the pain has gone for many months; we do not know if it will return.

D. Causalgic Pain Syndromes—These syndromes are seen frequently and are usually treated adequately by sympathetic blocks. In many instances, for various reasons such as patient preference or anticoagulants and the like, "blocks" cannot be used. These syndromes have in common: (1) vague area of distribution or at times a hysterical or stocking-glove distribution, (2) poor localization, (3) sensitivity to touch or temperature, especially cold, (4) burning character of the pain, (5) severe emotional reaction to the relentlessness of the pain, (6) vasomotor and/or trophic changes, (7) poor response to the usual analgesics. There also may be a need for something to control the pain which the patient can use as required. Thus, the TCS unit can be applied to the area of pain or over the area adjacent to the sympathetic ganglia involved. In these cases the unit's amplitude is usually used at a lower level and over a much longer period of time. Some patients have fallen asleep and left the unit on through the entire night. In general the frequency has been most successful at the faster rates, shorter duration and lower amplitude when used for longer periods of time. The use of somatic and sympathetic block as well as drugs, combined with the TCS unit, has been required on many occasions.

E. Ischemic Pain—The unit has been useful in pains of ischemic origin. These have been both subacute and chronic in nature. We fear the potential acidosis that might be present and even worsened in many of these cases, for example, the diabetic arterioscleotic foot pain with intermittent claudication, but feel that the unit might still be utilized for the causalgic pain syndrome. In some instances the unit has failed because of secondary muscle spasm.

F. Headache: (Tension Types)—We have not been very successful in the use of this unit in the classical tension headaches. We don't hesitate to try the unit but expect little help in a high percentage of cases. The same may be said of the migraine or migrinoid headaches. Many such sufferers are an absolute enigma. One tries drug after drug to stop the pain; one must not stop trying but in many instances is at a loss as what to use next.

G. Facial Pain Syndrome—These problems are in many instances extremely difficult to categorize. Many are associated with neuritic phenomena, referred pain, malocclusion syndromes, antral or oral diseases, etc. The unit should be tried over the area of referred pain or over the stellate ganglion area. On occasion we have used two units at the same time, one applied over the autonomic ganglia area and one over the area of referred pain.

When the pain has been well localized we have utilized an acupuncture needle and passed the current through the needle. In these instances the current amplitude, or strength, must be markedly diminished. Though the success rate is not high, trial of its use is justified and occasionally rewarding.

H. Sciatica and Disc Type Pain—These patients are among those most frequently seen in a pain center. Their pains extend from the cervical to the lumbosacral area. Most have not responded to local anesthetics, corticoids, traction, relaxants, etc. The pains may vary from mild, to sharp, stabbing in character, may be continuous to intermittent, may have

periods of remission; they may be aching and ill-defined. It is very difficult correctly to diagnose the true etiology or disease. They may really be a facet syndrome, a partial extrusion of a nucleus pulposus, a rheumatoid process, an osteoarthritic syndrome, a narrowing of intervertebral canal syndrome, radiculitis, neuritis, arachnoiditis, etc. In many instances one treats symptomatically. Rest is useful, so is traction, physical therapy, antiinflammatory agents, analgesics, and corticoids with and without local analgesics or anesthetics. We frequently use repetitive epidural or intrathecal sterile methylprednisolone acetate (Depo-Medrol®) and local anesthesia for this group of patients. The TCS is also an excellent supplement for this group of patients as in many instances it can stop the pain. It is applied over the site of the roots of the nerves involved or a segment or two above the distribution of the pain.

Combined therapy, that is: injections, with traction, rest, or transcutaneous stimulation and a relaxant is better than one method of treatment alone. Naturally one must be ever alert lest one miss a condition in which surgery or specific drug therapy is indicated. During the course of therapy we have had another extrusion of a disc (after several laminectomies); we have seen a mild radicular irritative pain become acute and, upon study, found a recurrent tumor which responded to surgical excision with excellent results.

I. Headache Syndromes—This condition like others though "chronic" and relatively static requires continuous alertness and a high index of suspicion lest one miss significant changes.

There are many diseases, syndromes, and conditions which cause headache symptoms. Many if not most are not clearcut as to etiology. In fact many may be of multiple origin. The "water intoxication" type, for example, associated with menstrual cycle may easily lead to a headache of essentially migraine type. The tension-type headaches are particularly troublesome to treat and present a real danger from drug abuse standpoint.

The TCS unit may be tried. When we first began using the unit for this application we had high hope but we now feel that our intial success was primarily a form of hypnosis or suggestion. Nevertheless it is worthy of a trial in many of the headache syndromes, especially those that are not responding to classical drug therapies. It is best to place the active electrode in the area of maximal pain. Also, in general, the stimulus should be kept mild, that is definitely below the discomfort level and for a minimum of half an hour after the pain has disappeared. In many instances the electrical therapy gives best results if combined with drugs. Especially useful is the stimulator technique, for drugs which alone do not control the pain may, when combined, be effective. This is extremely important because one may reduce if not eliminate the need for narcotic type drugs.

It is most important that the patient use the therapy, regardless of the type of headache or therapy, as early as possible. It is better medicine and better for the patient to abort an attack rather than to treat one that has already become severe. In many instances the patient will not be sure if an attack really is "coming on." Ideally, it is better not to know than to find out.

J. Postoperative Pain—At the present time a study is under way on pain control after "foot operations" comparing this unit to meperidine. The unit is used by placing a conductive tape about the foot as the active electrode and an indifferent electrode nearby. The unit is used whenever the patient desires to have it. It is put in place by the nurse of a single surgical group. It is the opinion of podiatrists concerned that most patients prefer the unit (as do the nurses) to the meperidine.

Other postoperative studies are in the planning stage. It would seem logical that if the unit works well in podiatry it should also work well in other areas of the body. Although at present it is all conjecture, it is certainly worth studying.

K. Carcinoma Pain—A significant number of patients with metastatic and/or inoperative carcinoma also have been treated by this unit. Experimental application is necessary. At times it is necessary to block primarily the somatic afferent flow while at other times it is preferable to block the visceral flow. It is difficult to predict which patient will get relief. But it is indeed gratifying to see patient requirements of meperidine in doses of 100 mgm every three hours decrease to an occasional dose every day or so. It is strange to see the panic expressed by some patients when the unit is removed to be used on another patient. Since many of these patients have "suffering" as well as "pain," adjunctive therapy of the tranquilizer type is very frequently useful. In general the active electrode should be placed cephalad to the dermatomes involved.

L. Miscellaneous Syndromes or Conditions—We have used the unit to treat pain syndromes such as glossopharyngeal neuritis. A needle of the Chinese acupuncture type can be inserted in an anteromedial direction to the styloid process originating midway between the anterior border of the tip of the mastoid and posterior border of the condyle of the mandible. The pain disappears in a matter of minutes. If an American needle is used, local anesthetics and corticoids may be injected at the end of the treatment.

In many instances we have used the instrument as a tool of suggestion therapy, or disguised hypnosis. Often it serves as a useful tool to permit time for further studies and logical procrastination.

CONCLUSIONS

We have presented our use of a relatively new instrument, the Tran-Q-lator, in the management of pain problems as seen in a very active pain center. Though the instrument has been refined and made more efficient it is of interest to note that a similar unit has been used by many other practitioners of the medical arts, other than the physician, for decades. Its basic value is that it has little potentiality for harm except in the patient with a pacemaker. The potentiality for the relief of many pain syndromes has been presented. Certainly it has the potentiality of abuse: if one treats a symptom without a definite etiology, then one may do harm by omission. But the overall value is exceptional in many cases. More work is necessary to better understand placement of the electrodes and the exact modus operandi of the unit. It is anticipated that the results will be useful in postoperative pain as well as the pain of childbirth.

REFERENCES

1. Shealy CN, et al: Electrical inhibition of pain by stimulation of the dorsal columns. Anesth Anal **46**:489-491, 1967
2. Shealy CN: Electrical inhibition of pain: Experimental evaluation. Anesth Analg **46**:299-305, 1967
3. Shealy CN: Dorsal column electrohypalgesia. Headache 9: 99-102, 1969
4. Shealy CN, et al: Dorsal column electroanalgesia. J Neurosurg **32**:560-564, 1970
5. Medical News: Screening procedure relieves chronic pain. JAMA **223**:968-969, 1973
6. Melzak R, Wall PD: Pain mechanisms: A new theory. Science **150**:971-979, 1965

MODIFIED LUDLOFF PROCEDURE FOR CONGENITAL DISLOCATION OF THE HIP: A PRELIMINARY REPORT

Mitchell B. Sheinkop
Timothy Lindquist
Allan Levine

ABSTRACT. A preliminary report of a method to achieve concentric reduction in congenital dislocation of the hip is presented. The method is applicable when conservative measures fail.

INTRODUCTION

The goal in treatment of congenital dislocation of the hip is a concentric stable reduction within an adequate acetabulum. In most cases this can be achieved by ten days to two weeks of traction followed by gentle manipulation under general anesthesia. The major complication of this form of treatment is aseptic necrosis of the femoral head.[1,2] It is now felt by most authorities who deal with children's orthopaedics that aseptic necrosis is directly related to the amount of force necessary to achieve reduction and the position used to maintain reduction in a cast.[3] Lorenz may be credited with having popularized this "frog" position. Smith-Petersen[5] popularized an open technique for achieving reduction when conservative measures failed. Children's orthopedists have been disappointed with the technique because of a very high incidence of aseptic necrosis of the head.[1,2] All structures in and around the hip have been incriminated as the etiological agent in preventing reduction of a dislocated hip (Fig. 1). Ludloff, working in Germany in 1910,[4] and more recently, Ferguson in this country, have theorized that the offending agent in preventing reduction is a constricted anterior capsule and contracted iliopsoas tendon.

This is a preliminary report to demonstrate a simple technique for open reduction of the hip when other methods fail, based upon anterior capsule release and iliopsoas tenotomy.

SURGICAL TECHNIQUE

The involved extremity is placed in flexion, abduction and external rotation. A skin incision (Fig. 2) is placed parallel

From the Department of Orthopaedic Surgery, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois and the Section of Orthopaedic Surgery, University of Chicago, Chicago, Illinois

Mitchell B. Sheinkop, M.D., Chief, Pediatric Orthopaedic Clinic; Assistant Attending Physician, Presbyterian-St. Luke's Hospital; Assistant Professor, Rush Medical College

Timothy Lindquist, M.D., Resident, Section of Orthopaedic Surgery, University of Chicago, Chicago, Illinois

Allan Levine, M.D., Resident, Department of Orthopaedic Surgery, Presbyterian-St. Luke's Hospital; Instructor, Rush Medical College, Chicago, Illinois

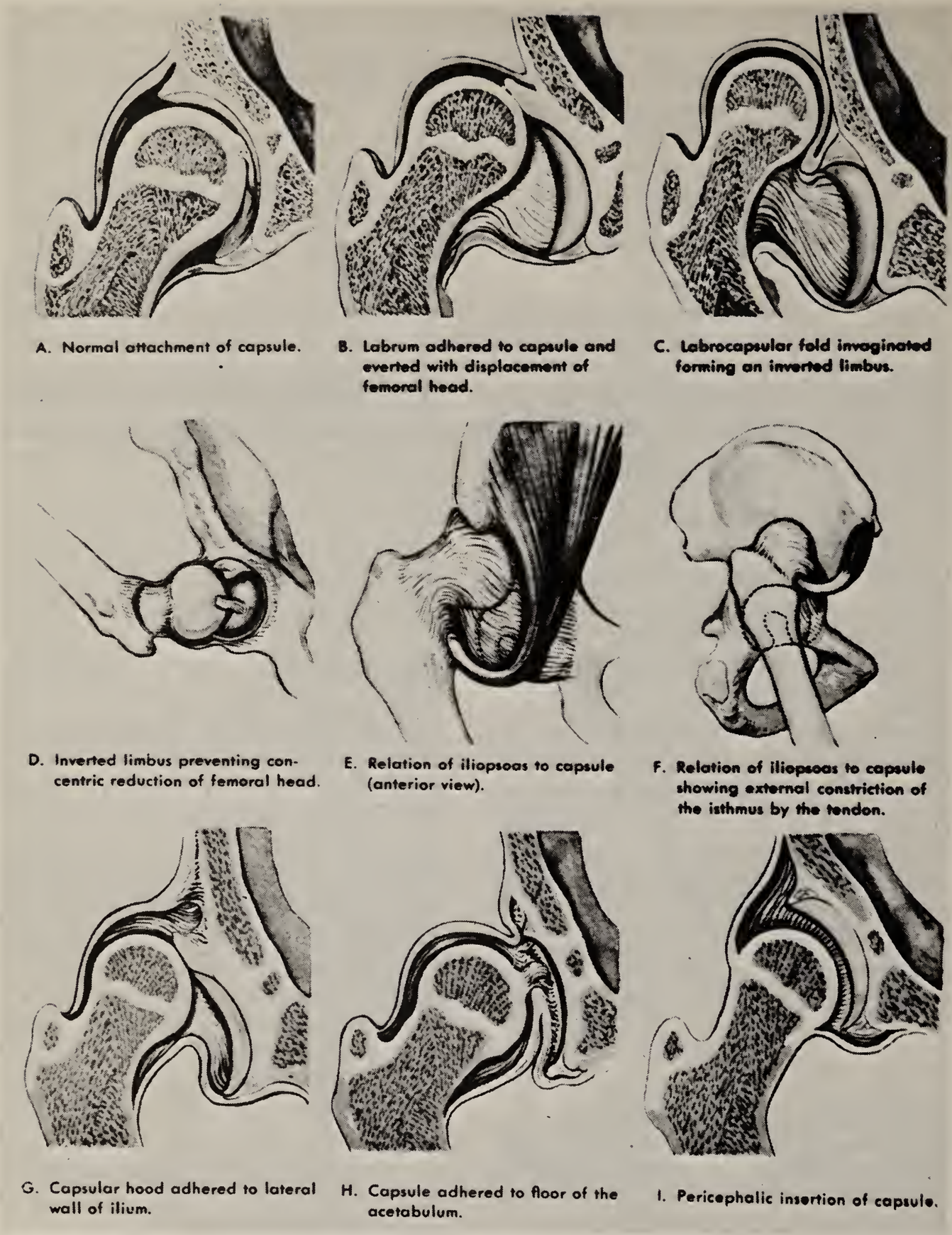

A. Normal attachment of capsule.
B. Labrum adhered to capsule and everted with displacement of femoral head.
C. Labrocapsular fold invaginated forming an inverted limbus.
D. Inverted limbus preventing concentric reduction of femoral head.
E. Relation of iliopsoas to capsule (anterior view).
F. Relation of iliopsoas to capsule showing external constriction of the isthmus by the tendon.
G. Capsular hood adhered to lateral wall of ilium.
H. Capsule adhered to floor of the acetabulum.
I. Pericephalic insertion of capsule.

Fig. 1—Obstacles to closed reduction of congenital dislocation of hip. (From: M. O. Tachdjian)

to the superior aspect of the adductor longus muscle beginning at its pelvic attachment. The interval between the iliopsoas muscle and the pectineus is identified and developed (Fig. 3). Several branches of the medial circumflex femoral artery may require ligation. The capsule of the hip is easily seen, after caudal retraction of the pectineus and cranial retraction of the iliopsoas and is

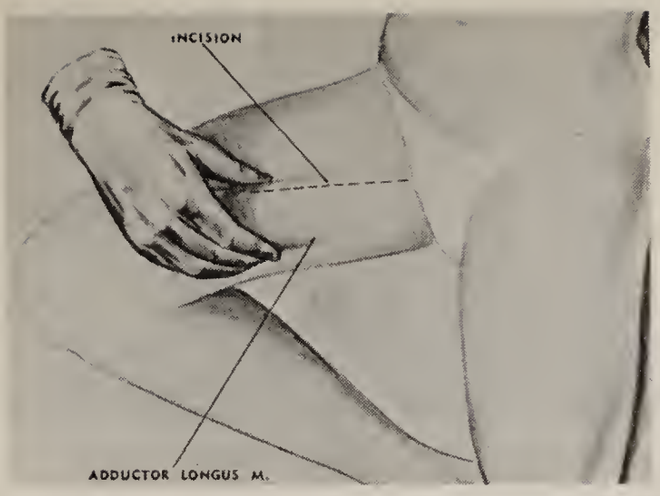


Fig. 2—The skin incision.

opened with a "T" incision.

Our present indications are: 1) congenital dislocation of the hip in a patient under two years which cannot be reduced by two weeks of traction and a gentle manipulation under a general anesthesia; 2) the unilateral arthrogrypotic dislocation; and 3) the congenital dislocation in the patient under age two, which after traction and manipulation, still is laterally displaced on X-ray (subluxation).

The following case report will serve to demonstrate the use of this rather simple technique for achieving reduction and maintaining reduction without force when gentle manipulation methods fail.

CASE REPORT

D.H., a white male infant was transferred to the Wyler Children's Hospital (Chicago) for evaluation and treatment of gross deformities of his extremities, at three months of age. His birth weight was 4.763 kg, and he was icteric. The patient's mother was a 30-year-old chemist, who took multivitamins, a diuretic, and a decongestant during her pregnancy. Her glucose tolerance test was within normal limits. The family history was negative for musculoskeletal disease.

On physical examination the patient was a large, mature, icteric newborn; length 50.17 cm, head circumference 38.5 cm, and chest circumference 38 cm. The anterior fontanelle was palpable and depressed. A high, arched palate was seen. Heart sounds were normal. No murmurs were heard. The abdomen was soft, protuberant, and had active bowel sounds. No masses were palpable. Genitalia were normal with bilaterally descended testes. A simian crease was present with a flexion posture of both elbows and wrists. All digits of the upper extremities showed intermittent hyperextension at the proximal interphalangeal joints with swan neck deformities. Skin creases over the elbows, wrists, fingers, hips, knees, ankles, and toes were absent or diminished in number. A severely restricted range of motion of all joints was noted. The hips were fixed in flexion and abduction and could not be brought to the neutral position. Both feet were in a talipes equinovarus position and were resistant to manipulation. Ortolani's test was negative.

Results of laboratory examinations included normal hemogram, urinalysis, and blood chemistries. Radiographs were consistent with a dislocation of the left hip (Fig. 4). Cast correction of the clubfeet was begun at the time of the patient's transfer. At four months of age the child

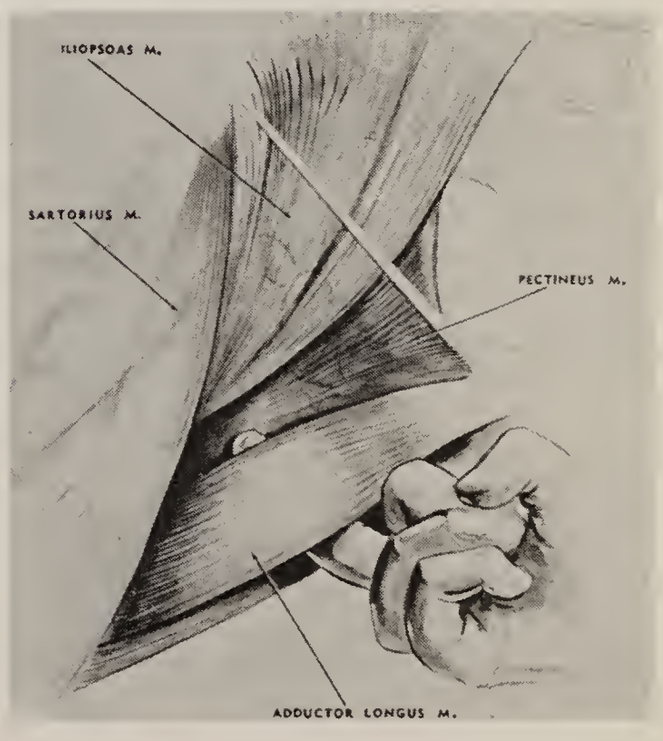


Fig. 3—The anatomy prior to developing the pectineus-iliopsoas interval.

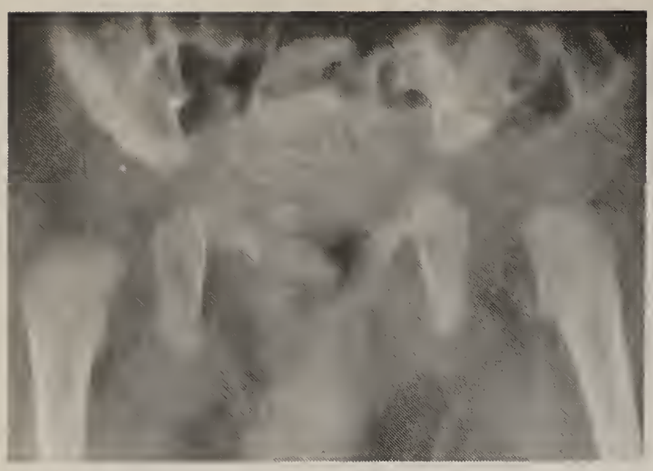


Fig. 4—X-ray of the pelvis compatible with a congenital dislocation of the left hip.

Fig. 5—X-ray of the pelvis compatible with a concentric reduction and ossification of the femoral epiphysis.

was readmitted and open reduction of the left hip was performed. The patient was managed in a one-and-one-half spica cast following surgery. The surgical wound healed without incident, and the cast was exchanged for an abduction hip orthosis at five months of age (Fig. 5).

SUMMARY

Early, gentle reduction of the congenital dislocation of the hip by the Ludloff procedure when traction fails, may completely eliminate the painful deformities of the hip in adulthood. The Ludloff procedure can be completed in a total of twenty minutes of operating time. One must recognize that in a tetratologic dislocation, or in the primary acetabular dysplasia with dislocation, an innominate osteotomy may still be necessary to assure development of a satisfactory acetabulum.

REFERENCES

1. Gage JR, Winter RB: Avascular necrosis of the capital femoral epiphysis as a complication of closed reduction of congenital dislocation of the hip. J Bone Joint Surg [Amer] **54A**:373, 1972

2. Salter RB, et al: Avascular necrosis of the femoral head as a complication of treatment for congenital dislocation of the hip in young children: a clinical and experimental investigation. Canad J Surg **12**:44, 1969

3. Trueta J: The normal vascular anatomy of the human femoral head during growth. J Bone Joint Surg [Amer] **39B**:58, 1957

4. Mau H, et al: Open reduction of congenital dislocation of the hip by Ludloff's method. J Bone Joint Surg [Amer] **53A**:1281, 1971

5. Smith-Petersen MN: A new supra-articular subperiosteal approach to the hip joint. Amer J Orthop Surg **15**:592, 1971

6. Ashley RK, Lasen LJ, James PM: Reduction of dislocation of the hip in older children—a preliminary report. J Bone Joint Surg [Amer] **54A**:545, 1972

PEDIATRIC RESEARCH IN RUSSIA: THE CLASSICAL PERIOD

Anatoly Bezkorovainy

ABSTRACT: Contributions to the field of pediatrics originated in many countries of the world, and Russia, before the First World War, produced a number of such outstanding pediatricians. Among the more accomplished Russian pediatric researchers were Filatov, the discoverer of infectious mononucleosis and the fourth disease; Gabrichevsky, the discoverer of the scarlet fever vaccine; Lunin, who was first to show the existence of vitamins; and Rauchfuss and Sokolov, whose work aided in the elucidation of the nature of pleurisy. The labors of a number of additional Russian researchers greatly contributed to the understanding of a number of other pediatric disorders.

The subject of the history of science or medicine may be approached through biographical accounts of individual personalities, as, for example, the article on Elie de Cyon in a recent issue of this journal.[1] Another, and in many cases, a more fruitful way of evaluating scientific progress is to look at a given field of endeavor as a whole, so that the accomplishments of many individuals can be examined and evaluated in terms of their contributions to modern scientific theories. The development of modern scientific and medical thought and practice is perhaps easiest to follow in the case of Russia, since these disciplines came to that country by royal edict rather than through a gradual development as it occurred in the West. We therefore have an excellent record of the first Russian physicians and scientists, the site of their training, and their influence, if any, on the development of future generations of doctors and scientists. It is thus known that the sciences were introduced into Russia by the establishment of the St. Petersburg Academy of Sciences in 1725 through the efforts of Peter the Great, and that the first medical school was established at a hospital in St. Petersburg in 1713 by the same ruler. It took, however, more than 100 years until locally-trained physicians and scientists began to make significant contributions to the world's scientific and medical pools of knowledge. However, at the dawn of the 20th century, several Russian universities and medical schools had reached a level of excellence on par with the best centers of learning in western Europe. This brief report is concerned with the accomplishments of some late 19th and early 20th century Russian physicians in the field of pediatrics.

Child mortality statistics of the pre-World War I era reveal that Russia was rather badly off in this regard: between 1879 and 1910, its child mortality rate dropped only from 296 per 1000 births per year to 266, whereas in Italy, it dropped from 214 to 142, and in France from 222 to 127 during the same period.[2,3] These figures tend to suggest that pediatric care in Russia was almost non-existent.

From the Department of Biochemistry, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois

Anatoly Bezkorovainy, Ph.D., Professor of Biochemistry, Rush Medical College, Chicago, Illinois.

However, this would be an oversimplification of the situation. In 1912 there were some 30 special pediatric hospitals in Russia, the oldest being the St. Petersburg Children's Hospital (1855), the Prince Oldenburg Children's Hospital in St. Petersburg (1869), and the St. Olga Children's Hospital in Moscow (1887). Every university in Russia had a pediatric hospital, to which patients could be referred by local doctors. In 55 of the 78 Russian provinces, there were foundlings' hospitals, the first ones having been established in 1764 in Moscow, and in 1770 in St. Petersburg by Catherine II. Child mortality rate in the provincial Simbirsk foundlings' hospital is said to have been 25 percent of that among the general populace. What, then, was the reason for the high child mortality rates in Russia before World War I? Hubert[3] states that a good 75 percent of such deaths were due to gastrointestinal disorders, which, in turn, were due to the peasant custom of feeding newborn infants black bread, cabbage soup, and "kvas" or fermented bread drink in addition to breast feeding. A distant second largest cause for the high child-mortality rates in Russia was infectious disease. Not much could be done about the gastrointestinal problem, because peasant customs and ways of life were difficult to change through friendly persuasion, and improvement could be expected only following the improvement of educational facilities in the countryside. The problem of infectious disease could, however, be improved by medical practitioners, and most pediatric researchers of Russia were, therefore, concerned with developing vaccines against childhood diseases and methods of therapy such as passive immunization.

Infectious diseases

One of the most distinguished Russian vaccine makers was G. Gabrichevsky (1860–1907), a professor at Moscow University and director of its Bacteriological Institute. He is best known for the development of a scarlet fever vaccine.[4] He cultured streptococci isolated from patients that had succumbed to the disease, heated the culture at 60°, then treated it with 0.5 percent phenol. The vaccine containing 0.02 to 0.03 ml of packed cells per ml of suspension was administered initially in a dose of 0.5 ml, then repeated twice with larger doses (0.75 to 1 ml) at seven to ten day intervals. The vaccine was tested at the St. Vladimir's Children's Hospital in Moscow, where only one case among 120 vaccinated children was noted. Among unvaccinated hospital-confined children, the morbidity was 3 percent.[5] Gabrichevsky was also involved in the production of diphtheria antitoxin, and children contracting the disease were routinely administered this antitoxin whenever a physician was available. This resulted in the lowering of the diphtheria mortality rate from 43 percent in 1890 to 25 percent in 1898 in the cities of Moscow and St. Petersburg.

Numerous other investigators published papers on the treatment of various childhood infectious diseases and complications thereof. Molchanov (b. 1868), of Moscow University, noted the involvement of the adrenals in diphtheria;[8] Troitzky, of Kharkow University, sought to treat scarlet fever with streptococcal antiserum, but only succeeded in enhancing the cardiac symptoms;[9] Vladimirov described cases of cardiac arrest during measles;[10] Sotov observed neurologic symptoms as a result of the same disease;[11] and Chernov published his views on the diagnosis and mode of treatment of spinal meningitis. He was a strong advocate of culturing spinal fluid obtained by lumbar puncture for diagnostic purposes.[12] A certain M. I. Afanassieff claimed in 1887 to have isolated the organism causing whooping cough; however, after the "re-discovery" of the bacillus by Bordet and Gengou in 1906, the two organisms proved to be different.[13]

Pleurisy

A more sophisticated series of investigations involved the diagnosis and treatment of pleurisy in children. The best known Russian pediatrician in this regard was Karl Andreevich Rauchfuss (1835–1915), a graduate of the Military-Medical Academy of St. Petersburg (1859), a later student of Rudolf Virchow, and the pediatrician to the Tsar's family. The Germans saw fit to publish an excellent biography of Rauchfuss following his death in spite of his service in the enemy camp during the First World War.[14] Rauchfuss is the discoverer of the so-called Rauchfuss Triangle which was used in the diagnosis of exudative pleurisy. He described this symptom at a meeting in 1903;[15] however, he claimed to have used it for the diagnosis of pleurisy in children for a number of years before the report. Rauchfuss noted that in children with exudative pleurisy there was on the back a triangular area, opposite to the area of effusion, which was dull to percussion, i.e., the percussion sounds were muted. The two sides of the triangle, at right angles to each other, were along the spinal cord and the base of the healthy lung, the latter being 2 to 8 cm in length, and the length of the other depending on the size of the area of effusion on the opposite side of the spinal cord. The apex of the triangle (situated on the spinal column) did not, however, correspond to the apex of the effusion area. Rauchfuss believed that the triangular area of dullness was caused by the displacement of the ava mediastinum by the effused lung into the healthy lung cavity. It should be mentioned that an area similar to the Rauchfuss triangle was observed at the same time by Grocco in adults. Thus the Rauchfuss triangle is frequently referred to as Grocco's sign.

Rauchfuss also is credited with the discovery of subglottal laryngitis[14] and the invention of the so-called Rauchfuss sling. The latter is a device which permits the changing of a patient's position without actually moving him. It is extremely useful in post-surgical cases, or where absolute immobility of the patient is necessary.

Among the congenital disorders described by Rauchfuss were the various cases of thrombosis involving the ductus arteriosus, pulmonary artery, or inferior vena cava.[16] He also reported a case of arterial stenosis, where the diameter of the aorta was only one-third that of the normal aorta. In addition, Rauchfuss described 25 cases in which the aorta originated from the right ventricle instead of the left ventricle, and where the pulmonary artery originated in the left ventricle. The symptoms of this disorder were cyanosis of the skin and mucous membranes and a hypertrophy of the heart without murmurs.[17]

Pleurisy was investigated by a number of other Russian physicians. S. Levashev, a University of Kazan professor, developed an operative method for the drainage of the exudate from the pleural cavity.[18] He noted that simple drainage of the abcess frequently led to complications with fatal outcome, and proposed to replace the drained fluid with a solution of 0.7 percent NaCl which had been carefully sterilized. The concentration of 0.7 percent NaCl was chosen because tests in animals indicated that NaCl concentrations of 0.2 to 0.6 percent and 0.75 to 1 percent caused the tetanization of muscles. The temperature of the fluid was 30°; however, if inflammation were present, the fluid was infused at a temperature of 12 to 15° with beneficial effects. The operation, which appeared to cause no pain to the patient, was performed by repeatedly draining the abscess and replacing the exudate by the saline in small portions. A single series of treatments was sufficient to cure exudative pleurisy and purulent pleurisy, if treatment was started at a sufficiently early stage of the disease. Replacement of the exudate by the saline was accompanied by an immediate drop in temperature, which, however,

later rose for a short period of time, and then dropped permanently. At the same time, the vital capacity was observed to return to normal.

Levashev's heroic method was applied to children by Alexander Kissel (1859–1938), a graduate of Kiev University and a student of Botkin (the "father" of Russian internal medicine). Of eight purulent pleurisy cases, Kissel was able to cure five, whereas the other three showed no improvement. He suspected lesions of tubercular origin in such cases.[19] Kissel was also one of the first pediatricians to recognize the connection between rheumatic disorders and cardiac complications. He reported the case of a boy who developed heart valve disease two years after recovering from a rheumatic condition involving the joints.[20]

Bacteriology of purulent pleurisy was investigated by Shkarin[21] of St. Petersburg, where the pleurisy was always found to coexist with pneumonia or bronchitis. In most instances, he was able to isolate pneumococci, either in pure culture, or mixed with streptococci, staphylococci, and tubercle bacilli.

The 19th century concepts of the etiology of pleurisy were modified by Dimitrii Sokolov, a pediatrics professor at the Women's Medical College in St. Petersburg and the director of its pediatric clinic. Using the newly-available method of examining patients with x-rays, he discovered that the exudate developed at the bottom of the lung, and in its final form had the shape of a triangle with the base at the bottom of the lung and the apex in the axillary region. The position of the fluid was not changed by changing the position of the patient. Previously it had been believed that such exudates had triangular shapes with the apex somewhere along the spinal column. Sokolov tested his finding by introducing water into the pleural cavities of cadavers, then taking x-ray pictures. The films showed the same patterns as those in his pleurisy patients.[22] Sokolov also constructed an apparatus, which he called the differential pneumograph,[23] designed to measure the degree of chest expansion on both sides of the chest during breathing. In a normal individual, both sides of the chest expanded and contracted in a perfectly parallel fashion during normal as well as forced breathing. Significant deviations from normal patterns were obtained in patients with various chest diseases, such as the lateral transposition of thoracic and abdominal viscera, stenosis of the larynx, cardiac hypertrophy, chorea, mediastinal tumors, pleurisy, and pneumonia. Many of the pneumographic patterns were correlated with chest x-ray films in the same patients, and were found to be in perfect agreement. The pneumograph is of course obsolete in today's medical practice, yet an examination of the curves obtained by Sokolov will reveal that they provide an excellent exercise in the field of chest physiology and could serve as a useful teaching tool in modern medical schools.

Vitamins

One of the earliest investigators to suggest the existence of vitamins and their role in nutrition was Russian pediatrician, N. Lunin (1854–1937), who, at the suggestion of G. Bunge, the pioneering investigator of iron metabolism, made an attempt to evaluate the significance of common salts in the nutrition of animals. Lunin was a graduate of the Dorpat University, and the work described below served as his Doctor of Medicine thesis. Lunin subsequently practiced pediatrics in St. Petersburg until his death. Georg Bunge held the opinion that the intake of metal ions by the mammalian organism was necessary in order to excrete the sulfur present in proteins in the form of sulfate. To test this theory, Lunin divided his mice into four groups:[24] the first received dried whole milk; the second received only distilled water; the third received ash-free casein, milk fat and sugar; and the fourth received the above ash-free diet with an amount of Na_2CO_3

equivalent to the amount of sulfur present in the casein. The first group of mice lived two and one-half months, and were all released from captivity. The second group survived two to four days. The third group lived for an average of 15 days, and the fourth group lived for an average of 26 days. Replacing the Na_2CO_3 by NaCl, or giving salt quantities greater than those required by the sulfur present in casein resulted in shortened life spans of the animals. Lunin then fed his fourth group of mice a mixture of salts equivalent to that present in whole milk, consisting of Ca, K, Na, Cl and F instead of the Na_2CO_3. The life spans of these animals averaged also 26 days. Lunin concluded that inorganic salts were indeed necessary for the proper nutrition of animals; however, the animals also required unknown organic factors other than fat, carbohydrate, protein, and ash for survival. He felt that perhaps such factors were like creatine, insofar that they were not metabolized by the organism. The unknown factors postulated by Lunin were, of course, vitamins, and it wasn't until 1906 that Hopkins made a similar suggestion, followed by Casimir Funk's definition of a vitamin in 1912.

Rickets was studied to a rather large extent in Russia because as many as 50 percent of the children were affected by it, in certain localities. The causes of this disease which were proposed by Russian investigators were as diverse and, in some cases, as exotic as those of other scientists, and ranged from environmental factors to malnutrition to aberrations in nitrogen metabolism. H. Kowarski of Vilna found that some 33 percent of the children in that city were affected by the disease, and that Jewish children were more prone to develop it than were gentiles.[25] He explained this on the basis that Jewish mothers were more reluctant to let their children play outdoors than were gentile mothers. He also found the disease more prevalent among those who lived in dark and damp quarters and were malnourished. Kowarski thus concluded that bad living conditions contributed to the development of the disease. He discovered a complication of rickets, which he called disuria spastica or difficulty in urination. Shkarin and Kuraieff attempted to explain the beneficial effects of the sun in terms of nitrogen metabolism in man.[26] Careful measurements of nitrogen intake and excretion during sun-bathing revealed nothing more than that in both normal and rachitic children the nitrogen retention was lowered during an exposure to the sun. No definite conclusion could be based upon these data. Probably the most logical proposal on the etiology and causes of rickets came from the work of J. A. Shabad from St. Petersburg, who felt that an inadequate intake of calcium was the cause of the disease.[27,28] Shabad carried out a remarkably detailed calcium, phosphorus, ash, and moisture analysis of normal and rachitic bones, and found a decrease of calcium and normal amounts of phosphorus in the latter. He then examined the mothers' milk of normal and rachitic children, and found that the mothers of rachitic children had an average of 63 mg of calcium per 100 calories, whereas those of normal children had 77 mg per 100 calories. He concluded that rickets was caused by the insufficient intake of calcium by the nursing infant. He excluded the possible use of cow's milk as a calcium supplement, because the latter, though higher in calcium content than human milk, was not able to provide calcium in the form which could be absorbed by the infant in sufficient quantity.

Tay-Sachs Disease

Exotic genetic diseases such as the Tay-Sachs disorder also were known in Russia. Kowarski described several cases, but noted that the disease very seldom was observed.[29] He attributed this to the fact not that people did not contract the disease, but to the fact that Russian physi-

cians were, for the most part, unfamiliar with it. As was the case with the English and American experiences, Kowarski's patients were all Jewish infants. He discovered an additional symptom of the disease—the total lack of a sense of equilibrium in the affected children.

The "father" of Russian pediatrics

We finally come to the man who is considered by many to be the father of Russian pediatrics, and has undoubtedly done most in popularizing this field in Russia and in training Russian pediatric practitioners. This individual was Nil Filatov, was first described by him in cow University, and later a professor of pediatrics there. He was the founder in 1892 of the Moscow Pediatric Society and served as its president for ten years.[30]

Filatov is credited with discovering the fourth disease and infectious mononucleosis, though, for some reason, he does not appear to have published papers dealing exclusively with these diseases. Instead, Filatov described both disorders either in papers dealing with the therapy of children's diseases in general, or in his pediatric texts. Perhaps for this reason, his discoveries went unnoticed by the outside world until both diseases were re-discovered, by Dukes in the case of the fourth disease, and by Pfeiffer in the case of infectious mononucleosis. Thus, the fourth disease, called Rubeola scarlatinosa by Filatov, was first described by him in 1885 in the Russian publication "Russkaya Meditsina" (No. 48), and later in his book *"Vorlesungen über akute Infektionskrankheiten im Kindesalter"* (1897, p. 382).[31] It was a scarlet fever-like disease, which lasted for a few days and resulted in full recovery of the patients. However, many such patients later came down with a *bona fide* scarlet fever. Dukes described the disease in 1900, terming it the fourth disease, and today it is known as the Filatov-Dukes disease.

Infectious mononucleosis was described by Filatov in 1887[32] as follows: *"Ich habe hier nicht die Adenitis im Auge, welche Entzündungsprozesse der tiefer liegenden Theile begleitet, z. B., der Mundhöhle, des Rachens, u. s. w., wobei nicht die Drüsen, sondern die zu Grunde liegende Krankheit das entscheidene Moment abgeben, sondern ich wünsche Ihre Aufmerksamkeit auf ein Leiden des Kindesalters zu lenken, welches freilich nicht in Büchern beschrieben wird und daher angehenden Aertzten gänzlich unbekannt ist, aber nichts destoweniger ziemlich oft im Leben vorkommt: ich meine namentlich die idiopathische Entzündung der lymphatischen Drüsen, welche am oberen Ende des Musc. sterno-cleido-mastoideus, d. h., unter dem Ohr und dem Proces. mastoideus, und hinter dem Angulus maxill. inferior liegen".** He called the disease idiopathic inflammation of the lymph glands. The disease was observed in children between the ages of two and four, and less frequently among adults. The fever remained five to ten days; however, the swelling persisted for two to three weeks. In 1889, Pfeiffer described the same disease, and it sometimes, perhaps unjustly, is referred to as Pfeiffer's disease.

Filatov wrote numerous articles and books, whose purpose appears to have been primarily educational, though, as noted, most such publications were replete with original observations. One such paper is his description of influenza in children,[33] in which he considered the

---

*"Here I do not have in mind the type of adenitis which accompanies inflammatory processes of those parts that are located more internally, *e.g.*, the oral cavity, the throat, etc., in which the basic disease and not the glands themselves constitutes the primary condition. I wish instead to direct your attention to a pediatric condition which, of course, is not described in the textbooks and would thus be unfamiliar to future physicians but which does nevertheless occur frequently in real life, namely, the idiopathic inflammation of the lymphatic glands which lie at the superior end of the sternocleidomastoid muscle, *i.e.*, below the ear and below the mastoid process, and posterior to the angle of the jaw."

fever, sniffles, and earache as the three most characteristic symptoms of the disease. In many cases, he noted, lesions (herpes) were observed on the mouth and nasal mucosa. Pneumonia was seen to be the most serious complication. Filatov's *"Klinische Vorlesungen über Kinderkrankheiten"* (Leipzig, 1901–1902) described each disease in terms of specific case histories. This work was a standard pediatric reference the world over, and may still be found in many American medical libraries, including the Rush library.

In conclusion it may be stated that pediatric services and research were well established in Russia before the first World War. Their benefits were rather poorly distributed among the bulk of the population since over 85 percent of Russia's population was rural at that time. Most Russian pediatricians, unlike their colleagues in the other medical specialities, were concerned with the containment and treatment of infectious disease. However, several individuals such as Gabrichevsky, Lunin, Filatov, and Rauchfuss will be long remembered for their original and fundamental contributions to other aspects in the field of pediatrics.

REFERENCES

1. Bezkorovainy A: Elie de Cyon: Historical note on a pioneering medical physiologist. RPSL Med Bull **11**:156, 1972
2. Winslow CEA: Public health administration in Russia in 1917. Weekly Publ Health Rep (Washington) **32**:2191, 1917
3. Hubert W: *Die gegenwärtige Stand der Frage über die Kindersterblichkeit in Russland und deren Bekämpfung. Arch f Kinderheilk* **57**: 351, 1912
4. Gabritschewsky G: *Ueber Streptokokkenvaccine und deren Verwendung bei der Druse der Pferde und dem Scharlach des Menschen. Centralbl f Bakt 1 Abt* **41**:419 and 844, 1906
5. Langowoy N: *Beobachtungen über die Wirkung der Scharlachstreptokokkenvaccine. Centralbl f Bakt 1 Abt* **42**: 362 and 463, 1906
6. Gabritschewsky G: *Ueber prophylaktische Massnahmen im Kampfe gegen Diphtherie. Centralbl f Bakt 1 Abt* **26**:490, 1899
7. Gabritschewsky G: *Zur Prophylaxe der Diphtherie. Centralbl f Bakt Ref* **36**:45, 1901
8. Moltchanoff W: *Zur Frage über die Rolle der Nebennieren in der Pathologie und Therapie der Diphtherie. Jahrb f Kinderheilk* **76**:200 (E-H), 1912
9. Troitzky JW: *Ueber die Funktionsstörungen des Herzens bei Scharlach. Arch f Kinderheilk* **45**:393, 1907
10. Wladimiroff GE: *Die Hospitalmasern und Sterbecasuistik nach Masern. Arch f Kinderheilk* **58**:346, 1912
11. Sotow AD: *Drei seltene Fälle von Complicationen bei Masern. Jahrb f Kinderheilk* **50**:1, 1899
12. Tschernow WE: *Zur Diagnose und Behandlung der sporadischen und epidemschen Cerebrospinalmeningitis. Jahrb f Kinderheilk* **67**:161, 1908
13. Klimenko WN: *Die Aetologie des Keuchhustens. Centralbl f Bakt 1 Abt* **48**:64, 1909
14. Heubner O: *Karl Rauchfuss. Jahrb f Kinderheilk* **83**:80, 1916
15. Rauchfuss C: *Ueber die paravertebrale Dämpfung auf der gesunden Brustseite bei Pleuraergüssen. Deutsch Arch f Klin Med* **89**: 186, 1906–07
16. Rauchfuss C: *Zur casuistik der Gefässverschliessungen. Virchow's Archiv* **18**:537, 1960

17. Etlinger N: *Casuistik der angeborenen Herzfehlern. Zeitschr f Kinderheilk* **6**:117, 1885

18. Lewaschew S: *Zur operativen Behandlung der exsudativen Pleuritiden. Deutsch Med Wochenschr* **16**:1229, 1890

19. Kissel AA: *Zur Behandlung der eitrigen Pleuritiden bei Kindern nach der Methode Prof. Lewaschew's. Jahrb f Kinderheilk* **50**:51, 1899

20. Kissel A: *Ein diagnostisch schwieriger Fall von Herzklappenerkrankung bei einem 12—jährigen Knaben. Jahrb f Kinderheilk* **53**:717, 1901

21. Schkarin AN: *Eitrige Pleuritiden bei Säulingen. Bakteriologie. Jahrb f Kinderheilk* **51**:650, 1900

22. Ssokolow D: *Zur Klinik der exsudativen Pleuritis bei Kindern. Jahrb f Kinderheilk* **67**: 70, 1908

23. Ssokolow D: *Der differentielle Pneumograph und seine Anwendung bei Kindern. Jahrb f Kinderheilk* **75**:265, 1912

24. Lunin N: *Ueber die Bedeutung der anorganischen Salze für die Ernährung des Thieres. Hoppe-Seyler's Zeitschr f Physiol Chem* **5**:31, 1881

25. Kowarski H: *Einiges über Rachitis. Jahrb f Kinderheilk* **67**:171, 1908

26. Schkarin A, Kurajeff W: *Beiträge zur Frage über die Wirkung von Solbädern auf den kindlichen Organismus. Zeitschr f Kinderheilk* **7**:413, 1913

27. Schabad JA: *Zur Bedentung des Kalkes in der Pathologie der Rachitis. Arch f Kinderheilk* **52**:47 and 68, 1910

28. Schabad JA: *Der Kalkgehalt der Frauenmilch. Zur Frage der ungenügenden Kalkzufuhr als Ursache der Rachitis. Jahrb f Kinderheilk* **74**:511, 1911

29. Kowarski H: *Sechs Fälle von Idiotia amaurotica progressiva familiaris infantilis. Jahrb f Kinderheilk* **76**:58, 1912

30. Rauchfuss C: *Nil Filatov †. Jahrb f Kinderheilk* **55**:517, 1902

31. *Abt's Pediatrics* **6**:421, 1925

32. Filatov N: *Ueber die Diagnose der Initialperiode der Fieberkrankheiten bei Kindern. Arch f Kinderheilk* **8**:180, 1887

33. Filatov N: *Influenza bei Kindern. Arch f Kinderheilk* **5**:357, 1884

ABSTRACTS

OF PUBLICATIONS BY THE STAFF

Biochemistry

Bezkorovainy A, Grohlich D: Reversible acylation of human serum transferrin. *Physiol Chem Physics 4:535, 1972*

Human serum transferrin was acylated with citraconic and maleic anhydrides, which resulted in the denaturation of the protein and a loss of its iron-binding activity. The acyl groups were then removed by mild acid hydrolysis and the native conformation, iron-binding activity, and antigenicity of the protein were restored. The recovery of the native protein was more efficient with the citraconylated species than with the maleylated material.

Booyse FM, Hoveke TP, Rafelson ME JR: Human platelet actin: isolation and properties. *J Biol Chem 248:4083-4091, 1973*

A rapid purification procedure for actin from human blood platelets is described. The isolated protein was found to be homogeneous by ultracentrifugation, polyacrylamide gel electrophoresis, and 3-methylhistidine analysis. The following physical parameters of the protein were established: sedimentation coefficient ($S^0_{20}\omega$) 3.09 S; partial specific volume (v), 0.718 ml g^{-1}; molecular weight ($M\omega$) from acrylamide gel electrophoresis, 46,100 ± 2,499; molecular weight ($M\omega^0$) from high speed equilibrium ultracentrifugation, 44,700 ± 2,590; and molecular weight ($M\omega^0$) of the reduced carboxymethylated protein, from high speed equilibrium ultracentrifugation, 45,000 ± 2,080. The amino acid composition of platelet actin is reported. ATP-salt-induced polymerization of platelet G-actin is concurrent with an increase in relative viscosity and release of inorganic phosphate. Addition of platelet actin to human platelet and rabbit skeletal muscle myosins enhanced the myosin ATPase activities and increased the relative viscosity of a platelet actin-platelet myosin protein mixture. In addition, electron micrographs of negatively stained (uranyl acetate) polymerized platelet actin show varying length, single filament-like F-actin polymers with a diameter of 61.5 ± 5.2 A. Platelet F-action also formed typical arrowhead-shaped complexes with rabbit heavy meromyosin. Finally, comparison of the CNBr-produced fragments of human platelet and rabbit skeletal muscle actions by polyacrylamide gel electrophoresis indicates distinct differences between these two proteins.

Legrand Y, Caen J, Booyse FM, Rafelson ME, Robert B, Robert L: Studies on a human blood platelet protease with elastolytic activity. *Biochem Biophys Acta 309:406-413, 1973*

The fractionation by ammonium sulfate precipitation and gel filtration on Sephadex G-150 of Triton X-100 extracts of human blood platelets is described, as well as the determination of the enzymatic (proteolytic and esterolytic) activities of the fractions obtained with ^{125}I-labeled elastin, hemoglobin and synthetic substrates $AcAla_3OMe$, BzArgOEt and AcTyrOEt.

Activity towards $AcAla_3OMe$ was significantly higher in all fractions than that towards AcTyrOEt and BzTyrOEt.

The highest specific activity towards $AcAla_3OMe$ and ^{125}I-labeled elastin was obtained in the 2nd Sephadex peak of the 70 percent ammonium sulfate precipitate. The increase in specific activity towards $AcAla_3OMe$ was of the order of 1200, with respect to the Triton extract.

The 2nd Sephadex peak of the 70-percent ammonium sulfate precipitate gives three bands on acrylamide electrophoresis, the 2nd band containing all elastolytic activity.

Preincubation with trypsin significantly increases the ^{125}I-labeled elastin splitting activity of the Triton extract and of the 40-percent ammonium sulfate precipitate. No, or only a very light activation, was observed in the 70-percent ammonium sulfate precipitate.

These results suggest the presence of an inactive precursor in the 40-percent ammonium sulfate precipitate and of an activated protease in the 70-percent precipitate.

The high specific activity of the purified fraction (2nd peak of 70-percent ammonium sulfate precipitate) with $AcAla_3OMe$ and ^{125}I-labeled elastin as substrate, as well as the absence of activity on other substrates (hemoglobin BzArgOEt and AcTyrOEt) justified the denomination suggested of "platelet elastase" for the protease in this fraction.

Miller RJ, Bezkorovainy A: The effects of irradiation on human serum transferrin. *Radiat Res 54:212-221, 1973*

Iron-free and iron-saturated human serum transferrins were irradiated at doses of 1-10 x 10^6 rads, and the resulting changes in their physical parameters were measured. It was found that tyrosyl groups and disulfide bonds were perturbed at the lowest levels of irradiation. Next, a perturbation of the iron-binding site was observed. Gross denaturation and aggregation of the protein molecules were observed only at the highest doses of irradiation. The effects of irradiation on the iron-binding sites were retarded by the presence of the iron therein, which possibly acted as an energy sink.

Dermatology

Malkinson FD, Griem ML, Marianovic R: Effects of hydroxyurea and radiation on hair matrix cells. *Cell Tissue Kinet 6:395-405, 1973*

Investigations were undertaken in CF_1 mice to study the effects of hydroxyurea (HU) on hair matrix cell kinetics, and to assess the effects of combined administration of HU and irradiation on induction of temporary alopecia. HU 100 mg/kg was administered intraperitoneally, and each animal received tritiated thymidine 0.5 μCi/g 30 minutes before biopsy. Serial biopsies were taken up to 48 hours after drug administration. Autoradiographs of anagen follicle squashes revealed sharp reductions in mitotic and labeling indices within 30 minutes. Depressed mitotic indices of 0.6-0.9 percent at 1 to 4 hours returned to normal (2.3 percent) after 6 hours, followed by cyclic mitotic "overshoot," and were preceded by parallel changes in the labeling indices. HU-induced cellular damage was most marked 4 hours after HU injection, with almost complete recovery from injury observed at the 24-hour interval.

The effects of varying the time intervals from 1 to 12 hours between HU administration and irradiation (650 rads) after injection of HU 1200 mg/kg were examined. Hair loss was measured seven days later by photomicroscopy. Cyclic maximum alopecia was found at the 1-to-5 and 8-to-12 hour intervals, with relative "protection" occurring at the 6-to-7 hour time periods.

Orthopedics

Belytschko T, Schultz AB, Kulak RF, Galante JO: Numerical Stress analysis of Intervertebral Disk. *Amer Soc Mech Eng Paper No. 72-WA/BHF-12, Nov., 1972*

An axisymmetric finite element model is employed for the study of the behavior of an intervertebral disk under axial loading. By matching experimental results on the overall

behavior of the disk, orthotropic linear material constants are obtained for the annulus fibrosus. Results are then presented on the effects of material properties and geometry on the stress-distribution and intradiskal pressures. It is shown that (1) degenerative changes associated with loss of elasticity have little effect on the intradiskal pressure, while annular tears result in reduced pressure in agreement with clinical observations; (2) that material properties of the annulus obtained by direct measurement far underestimate the strength of the material; and (3) reasonable predictions of variations of disk stiffness with vertebral level can be made on the basis of geometry.

Galante J, Rostoker W: Corrosion-related failures in metallic implants. *Clin Orthop 86:237-244, 1972*

Four specimens each were prepared of the following materials with a special stress-point design: Vitallium, 316L stainless steel, unalloyed titanium, Ti 6 per cent Al 4 per cent V, and Zircalloy. No evidence of stress-corrosion cracking was found in any specimen. Isolated pits were found on three specimens of Ti 6 per cent Al 4 per cent V, and in one of Vitallium and one of stainless steel. A titanium specimen showed light multiple pitting. The least tissue reaction was found around the Vitallium, stainless steel and unalloyed titanium coupons.

Galante J, Rostoker W: Fiber metal composites in the fixation of skeletal prosthesis. *J Biomed Mater Res Symposium 3:47, 1973*

To serve as a component of a load-bearing skeletal prosthesis, a porous material should offer the following attributes: (1) pore channels over 100 μ in diameter; (2) continuity of pore channels; (3) matrix material inert and compatible with animal tissues; (4) manufacturable as thick coatings or thin-walled complex surface assemblies; (5) manufacturable to precision dimensions; (6) large compliance comparable to bone; (7) crack resistance, particularly under impact.

A porous composite was manufactured by molding and sintering short metal fibers, which fulfilled all of these requirements. The composite was manufactured both with titanium and Vitallium fibers.

Experimental implants were performed in dogs and rabbits indicating peripheral bone formation around the implant at two weeks, and penetration from three weeks on. Shear strength values at the prosthesis-bone interface were in the range of 20 kg/cm^2 three weeks after implantation.

Femoral prostheses implanted in dogs revealed fixation by bone formation and maintenance by bone ingrowth up to one year following implantation.

Massive incorporation with bone of skeletal segmental replacements for the baboon's femur were seen up to three months following implantation.

Practical problems that can be encountered with the use of porous fiber metal composites for prosthesis fixation relate to: (1) the possibility of long-term corrosion occurring in an implant with a very large surface area: (2) technical problems with implantation requiring intimate contact between the fiber metal surface and the bone and (3) the difficulties in removing an implant which has failed for mechanical reasons requiring that a device manufactured using fiber metal composites for fixation be absolutely failure-free from a mechanical viewpoint.

Galante JO, Rostoker W: Wear in Total Hip Prostheses: an experimental evaluation of candidate materials. *Acta Orthop Scand Supp 145:1-26, 1973*

A laboratory study of wear applied to human hip joint prosthesis was presented.

A wear testing machine was developed incorporating the following characteristics:

1. Disc-on-plate specimen configuration.
2. Alignment and concentricity characteristics of a precision surface grinder.

3. Fixture for dressing specimens in place.

4. Direct load range of 0 to 270 kg. Continuously variable speed between 500 and 20,000 cpm.

5. Immersion of sliding interface in circulating solution at controlled temperature.

6. Direct and continuous monitoring of wear depth and co-efficient of friction.

The materials were studied at sliding speeds of 635 and 8900 cpm, in a stress range varying between 2.1 to 6.9×10^6nt/m^2. They were immersed in water at 37° C.

Over 25 different materials and combinations of materials were evaluated including ceramics, polymers and metals. The following conclusions were derived:

1. For most materials wear rate is independent of coefficient of friction. High wear rates can be associated with low coefficient of friction and vice-versa.

2. The wear rates of ceramics including Pyroceram, Aluminum Oxide, Silicon Carbide and Boron Carbide were too high and not acceptable for use in total joint prostheses.

3. RCH 1000 (ultra high molecular weight polyethylene) bearing against Vitallium offered the lowest wear rates of the commercially available materials.

4. The choice of metal in a metal-on-plastic bearing is important in determining wear rates. Titanium and its alloys produced very high wear rates. Stainless steel bearing against RCH 1000 produced higher wear rates than Vitallium. The process was thought to be related to a surface corrosion phenomenon.

5. Wear rates were found to be closely dependent on contact stress. This is an important consideration in prosthetic design where the size of the femoral head and hence, contact stresses can be varied over a wide range.

6. A material was developed consisting of ultra high molecular weight polyethylene with 25 percent graphite powder. This material exhibited wear rates between 1/7th and 1/30th of those obtained with ultra high molecular weight polyethylene alone. It is suggested that its use in a total hip joint prosthesis would satisfy the requirements of a very successful and long service life.

Lembert E, Galante, J, Rostoker W: Fixation of skeletal replacement by fiber metal composites. *Clin Orthop 87:303-310, 1972*

Implantation of an open pore aggregate of sintered titanium fibers resulted in deep ingrowth of bone. Pore size variations of 190 μ to 390 μ did not affect the strength of fixation or the amount of bone penetration. The strength of fixation of sintered fiber metal implants after six weeks was found to be in the same range as that obtained using self-curing acrylic. The effect of weightbearing was studied in femoral head prostheses implanted in eight dogs. Fixation to the femur and bone ingrowth into the fiber metal composite were successfully maintained up to one year following implantation.

Pathology

Eisenstein R, Sorgente N, Arsenis C, Kuettner KE: Vitamin D Effects on Tissue and Serum Lysozyme. *Arch Path 94:479-485, 1972*

Hypervitaminosis D induces an increase in diffusible lysozyme in rat serum, aorta, and epiphyseal growth plate. The amount of lysozyme in the aorta correlates best with the phosphate concentration in this tissue. This suggests that it accumulates after mineralization has begun since phosphate accumulates after calcium in this form of experimental calcification. In normal aortas, lysozyme appears to be primarily a lysosomal enzyme while in calcifying aortas it apparently is concentrated in extracellular sites of mineralization. In rachitic rats, the amount of lysozyme in epiphyseal growth plate diminishes. When viewed in the context of current knowledge, the data suggest that the role of lysozyme in calcification is more directly related to its involvement with an as yet unidentified binding substance in extracellular tissue than to any enzymatic activity or to the process of calcification itself.

Shakibi JG, Diehl AM: Postnatal development of the heart in normal Swiss-Webster mice. *Lab Anim Sci 22:668-683, 1972*

The hearts of 140 normal newborn Swiss-Webster mice were examined by serial section, and two were found to have congenital heart disease. The cardiovascular anomalies consisted of single cases, one lacking a tricuspid valve and one with a ventricular septal defect. The heart of the newborn Swiss-Webster mouse develops further after birth. The septal cusp of the tricuspid valve and the membranous portion of the ventricular septum are formed after birth, and valvulae venosae are resorbed in the first week of extrauterine life.

Pediatrics

Brazie JV, Lubchenco LO: The newborn and premature infant. From: *Current Pediatric Diagnosis and Treatment, Eds Kempe CH, Silver H, O'Brien D, Lange, Los Altos, 1972, pp. 40-88*

The newborn period is usually defined as the interval from birth to age 28 days, though the main clinical emphasis is on the infant's initial nursery stay.

It is obvious that the events leading up to and including birth are vital to the succeeding 28 days, and adequate knowledge of the infant's prenatal and birth history is essential in providing newborn care.

Every newborn infant should be considered a patient in his own right and not a boarder resulting from his mother's admission. Someone must be responsible for the care of the newborn infant from the time of delivery to ensure his satisfactory adjustment to extrauterine life. It is no longer appropriate to organize newborn nurseries only for the care of well newborns who make these adjustments with minimal difficulty. In order to focus care on the potentially sick infant, the newborn service must have trained personnel available who can anticipate and recognize significant symptoms and signs and institute appropriate diagnostic and therapeutic measures. The specific treatment and general supportive care of the sick newborn infant should be thoroughly understood, and adequate therapeutic facilities must be available.

Certain illnesses can be anticipated before delivery. If the baby is likely to require special care soon after birth, delivery should be planned in or near the hospital where that care is available. Transfer of sick newborns to another hospital for intensive care may result in considerable delay in initiating optimal care, and the transfer itself may introduce additional hazards. Any hospital that assumes the responsibility for delivering newborn infants must provide adequate staff and equipment to manage urgent newborn problems. If the baby's subsequent needs exceed the hospital's capabilities, transfer to a special care newborn center will be necessary.

Goodwin CD, Levy HB, Caldwell RG, Johnson FR, Christian JR: Treatment of the premature infant by hyperalimentation: a preliminary report. *Pediat Digest 14:23-35, 1972*

Hyperalimentation has been studied in a series of 10 premature infants. Complications caused by hyperalimentation have been minimal and there has been no mortality attributable to the hyperalimentation.

By the use of hyperalimentation to supplement oral feedings, the infants showed a greater propensity to a significantly positive nitrogen balance and appear to have gained strength more rapidly and required shorter periods of hospitalization with the inherent risk of exposure to infection from resistant organisms. The need for large oral feedings with a risk of aspiration and the impairment or respiration caused by gastric distention have likewise been avoided.

In a short follow-up period the infants compared favorably in growth and motor development with normal, term babies of the same age.

The preliminary results in this small series suggest that the technique is helpful in management of the premature infant and that it merits further investigation.

Hyde JS, Floro LD, Vithayasai V: Chronic and high-risk asthma in children. *Amer J Dis Child 123:541-546, 1972*

High-risk asthma signifies probable harm to the patient either because of periods of prolonged ventilatory defect, a clustering of manifestations indicating a poor prognosis, or severe life-threatening attacks. Ninety-five children referred to a university diagnostic center were classified as high-risk and were selected from others with chronic asthma. These were observed at monthly intervals for at least two years. Ongoing disability usually resulted from failure to establish and eliminate causes and excessive dependence on adrenergic aerosols or corticosteroids. Case reports include patients with aspirin intolerance, allergic asperigillosis, α_1-antitrypsin disease, misuse of adrenergic aerosols, and the effect of newer therapeutic agents in care of formerly unresponsive patients.

Hyde J, Isenberg PD, Floro LD: Short- and long-term prophylaxis with cromolyn sodium in chronic asthma. *Chest 63:875-880, 1973*

Thirty-eight children with chronic asthma (mean age 10.2 years) were given cromolyn sodium and placebo in a double-blind crossover study of eight weeks' duration. A statistically significant difference ($P < .005$) in physician's ratings, in favor of cromolyn therapy was found for both sequences. Subsequently, cromolyn was given prophylactically for at least 12 months to 33 of these children. Compared to the previous year, improved performance in physical exercise, lessened school absenteeism, reduced hospitalizations and improved sleep patterns appeared to warrant the continued use of cromolyn. A decreased frequency of attacks in 26 of 33 and reduced need for bronchodilators in 25 of 33 children occurred as well as an improvement of peak expiratory flow rates measured during airborne pollen and mold seasons. Hepatic, hematologic and renal disturbances were not noted. There were no voluntary complaints of side-effects.

Isenberg PD, Hyde JS, Stine, RH: Peak expiratory flow rates in chronic asthma: A gauge of progression and improvement. *Amer J Dis Child 125:341-345, 1973*

Because there is doubt over the usefulness of the peak expiratory flow meter in assessing the course of chronic asthma, 55 children aged 6 to 18 years were studied over a period of 12 months. All children who were receiving cromolyn sodium prophylaxis were tested at monthly intervals, with the peak expiratory flow rate (PEFR) meter and at three-month intervals by conventional spirometry.

The patients were separated into three groups according to their monthly PEFR results: (1) values always within normal limits; (2) values fluctuating between normal and abnormal ranges; and (3) values consistently subnormal. A "drop-off" of at least 15 percent in PEFR was observed with 25 of the 55 children when five successive expirations were measured.

The PEFR, the forced expiratory volume in the first second, and the maximum voluntary ventilation correlated well ($P = .001$) in all cases. Pulmonary function values in 16 patients (29 percent) failed to show the expected return to normal during the one-year period.

Lewy JE, Cabana EC, Repetto HA, Canterbury JM, Reiss E: Serum parathyroid hormone in hypophosphatemic vitamin D-resistant rickets. *J Pediat 81:294-300, 1972*

Serum parathyroid hormone (PTH) was measured in five children with untreated, active hypophosphatemic vitamin D-resistant rickets before, during, and after an infusion of calcium. During the calcium infusion, serum PTH decreased while the tubular resorption of phosphate increased. Although these data clearly indicate that some degree of hyper-

parathyroidism accompanies the disease, it is apparent that the degree of hyperparathyroidism recorded in these studies is not sufficient to explain the severity of the phosphaturia. One of the basic defects in the disease may involve excessive sensitivity of the renal tubule to the phosphaturic effects of PTH.

Lubchenco LO, Searls DT, Brazie JV: Neonatal mortality rate: relationship to birth, weight and gestational age. *J Ped 81:814-822, 1972*

Data on neonatal mortality rates, by birth weight and gestational age, are presented in a variety of ways to indicate their usefulness in everyday practice. The conventional rates by birth weight groupings have been useful in the past, but data by both birth weight and gestational age are necessary for evaluation of current perinatal practices. Mortality rates in small blocks and in curvilinear zones by birth weight and gestational age are useful in evaluating the outcome of individual pregnancies and newborn infants. Each of these methods serves a specific need, and the advantages of each are described. The importance of using both birth weight and gestational age, when reporting mortality rates in neonatal populations, is emphasized.

Mehta DM, Flanagan MJ, Christian JR: Perineal ectopia of the testis. *Pediat Digest, April 1972, pp 43-45*

A patient with perineal ectopia underwent surgical correction.

Various ectopic positions of the testis should be considered before a diagnosis of cryptorchidism is made.

Schwartz DD: Chronic asthma in children. *JAMA 222:485, 1972*

In contrast to many disease conditions that show a precipitous rise in patients over the age of 45 years, allergic disorders exert an equal impact on those under 45. Data from the National Health Survey in 1966-1967 show that, as a cause of limitation of activity in persons under 45, asthma-allergic rhinitis is second or third only to impairments of back and spine, and mental and nervous conditions. Perhaps even more significant, asthma-allergic rhinitis was the leading cause of limitation of activity among nearly 30 percent of persons under age 17.

The syndrome of recurrent episodes of wheezing, shortness of breath, and coughing is acceptable as a description of asthma. Asthma is a disease with concise manifestations. Bronchial hyper-reactivity is a consistent, usually reversible, characteristic of this disease, but for the chronic case, mucosal edema and mucus production perists. Pathogenic mechanisms of asthma vary individually with no two people being exactly alike, with the finding of different causes, occasionally purely biochemical, others environmentally induced, and most often a mixture.

High-risk chronic asthma reported by Hyde, Floro and Vithayasai included a group of patients who had a clustering of manifestations usually associated with unfavorable prognosis. Examples were allergic aspergillosis, heterozygous α_1-antitrypsin defect, egg albumin-sensitivity in eczematous children with early onset of asthma, and aspirin intolerance. By coincidence these patients were sometimes atopic. A second high-risk group had life-threatening attacks of asthma. Representative factors included aspirin intolerance, misuse of adrenergic aerosols, and steroid dependency. Other high-risk asthmas were observed by looking for interim bronchospasm. Many of these children had grossly hyperinflated chests, school absenteeism exceeding three weeks per year due to lower-respiratory tract disease.

Children, as well as adults with chronic asthma, should be subjected to more complete diagnostic evaluations to establish the causes of their ongoing disability. No field of scientific medicine today has greater opportunities to bring new knowledge for the relief of patients and the prevention of their suffering.

Saxena VS: Seminoma of the testis. *Amer J Roentgen 117:643-652, 1973*

During the period of 1947 to 1969, 77 patients with pure seminoma of their testes were seen at Brooke General Hospital, Fort Sam Houston, Texas.

Most of the patients were younger than reported by other authors. The right and left testis was involved with almost equal frequency.

All of our patients except two had a Stage I disease. Orchiectomy on the affected side was the method of biopsy routinely in all patients.

In this series no difference was noted in the survival rates of the patients who have had different kinds of treatments such as: retroperitoneal lymph node dissection and irradiation; irradiation to the abdominal paraaortic lymph nodes; and irradiation only of the abdominal paraaortic, mediastinal, and left supraclavicular regions.

The retroperitoneal lymph node dissection in pure seminoma of the testis has no role in its management.

There are also enough reasons to believe that routine irradiation of the mediastinum and the left supraclavicular region in a Stage I seminoma of the testis is not warranted.

It is suggested that a great effort should be made to stage these patients with pure seminoma before any definite treatment is started. In a truly Stage I disease the cure rate should be close to 100 percent, if managed adequately.

Vijungco J, Phillips R, Hendrickson FR, Millburn LF: Stage I and II non-Hodgkin's lymphoma: Results of regional radiation therapy. *Amer J Roentgen 117:45-49, 1973*

A review of the literature and our own work suggests that the Clinical Stage I and II non-Hodgkin's lymphoma deserves thorough pretherapeutic evaluation and aggressive regional treatment, and that, when this is done, a favorable prognosis can be expected.

INDEX TO ARTICLES AND AUTHORS IN MEDICAL BULLETIN
1972

ARTICLES

Abstracts of Publications by the Staff: Vol. 11, No. 1, pp. 42-45, Jan., 1972; Vol. 11, No. 2, pp. 78-86, Apr., 1972; Vol. 11, No. 4, pp. 161-168, Oct., 1972

Cancer: *See,* Familial Medullary Carcinoma and Parathyroid Adenoma without Pheochromocytoma: Report of Two Cases; Metabolic Syndromes Associated with Neoplasia; Non-Hodgkin Lymphomas An Assessment; Quantitation of Anticancer Agents; Remote Hematological Manifestations of Malignant Disease; Remote Effects of Cancer on the Nervous System: A Review; Renal, Gastrointestinal, and Musculoskeketal Manifestations of Neoplasia

Chicago: Patients and Providers, or Who Takes Care of Whom? Irene R. Turner, Vol. 11, No. 1, pp. 35-41, Jan., 1972

de Cyon, Elie: Historical Note on a Pioneering Medical Physiologist. Anatoly Bezkorovainy, Vol. 11, No. 4, pp. 156-160, Oct., 1972

Familial Medullary Carcinoma and Parathyroid Adenoma without Pheochromacytoma: Report of Two Cases. William S. Markey, Will G. Ryan, Steven G. Economou, Glen W. Sizemore, and Claude D. Arnaud, Vol. 11, No. 4, pp. 151-155, Oct., 1972

Index to Vol. 11: Vol. 11, No. 4, pp. 169-170, Oct., 1972

Introduction to Symposium on Remote Effects of Malignant Neoplasms. Charles P. Perlia and Arthur H. Rossof, Vol. 11, No. 3, p. iii, July, 1972

Medea, The: *See,* Personality Development as Illustrated by The Medea

Metabolic Syndromes Associated with Neoplasia: Ira J. Piel, Arthur H. Rossof, Janet M. Wolter, and Theodore B. Schwartz. Vol. 11, No. 3, pp. 123-131, July, 1972

Non-Hodgkin Lymphomas, The—An Assessment: Jose Vijungco, Lowell F. Millburn, Robert F. Slayton, and Frank H. Hendrickson. Vol. 11, No. 2, pp. 72-77, Apr., 1972

Personality Development as Illustrated by the Medea. Richard Koenig, Vol. 11, No. 1, pp. 31-34, Jan., 1972

Physician, The, the *Suicidococcus Contagiosa* and Medical Practice: H. L. P. Resnik, Vol. 11, No. 2, pp. 66-71, April, 1972

Prostate: *See,* Surgery of the Prostate, Recent Developments in

Prosthesis: *See,* Use of Fiber Metal Composites as a Method of Fixation of Skeletal Prosthesis

Quantitation of Anticancer Agents. Frederick A. Valeriote, Vol. 11, No. 2, pp. 51-65, Apr., 1972

Radiology of the Temporal Bone: Recent Applications of Laminography. Jerry P. Petasnick and Michael S. Huckman, Vol. 11, No. 1, pp. 10-17, Jan., 1972

Remote Effects of Cancer on the Nervous System, the: A Review. Robert R. McKendall and Maynard M. Cohen, Vol. 11, No. 3, pp. -113, July, 1972

Remote Hematological Manifestations of Malignant Disease. Mark Tuckfelt and Frank E. Trobaugh, Jr., Vol. 11, No. 3, pp. 114-122, July, 1972

Renal, Gastrointestinal, and Musculoskeletal Manifestations of Neoplasia. Arthur H. Rossof and Charles P. Perlia, Vol. 11, No. 3, pp. 132-140, July, 1972

Suggestions to Authors: Vol. 11, No. 1, p. 48, Jan., 1972; Vol. 11, No. 2, p. 87, Apr., 1972; Vol. 11, No. 4, p. 171, Oct., 1972

Suicide: *See,* The Physician, the *Suicidococcus Contagiosa,* and Medical Practice

Surgery of the Prostate: Recent Developments in. Malachi J. Flanagan, Vol. 11, No. 1, pp. 3-9, Jan., 1972

Symposium: The Remote Effects of Malignant Neoplasms. Vol. 11, No. 3, July, 1972

Temporal bone: *See,* Radiology of the Temporal Bone. Recent Applications of Laminography

Treatment of the Premature Infant by Hyperalimentation: A Preliminary Report. Charles D. Goodwin, Howard B. Levy, Richard G. Caldwell, Joseph R. Christian, and Frank R. Johnson, Vol. 11, No. 1, pp. 18-30, Jan., 1972

Urban Medicine: *See,* Chicago: Patients and Providers, or Who Takes Care of Whom?

Use of Fiber Metal Composites as a Method of Fixation of Skeletal Prosthesis, The. Jorge O. Galante and William Rostoker, Vol. 11, No. 4, pp. 143-150, Oct., 1972

AUTHORS

Arnaud, Claude D, Vol. 11, No. 4, pp. 151-155, Oct., 1972

Bezkorovainy, Anatoly, Vol. 11, No. 4, pp. 156-160, Oct., 1972

Caldwell, Richard G, Vol. 11, No. 1, pp. 18-31, Jan., 1972
Christian, Joseph R, Vol. 11, No. 1, pp. 18-30, Jan., 1972
Cohen, Maynard M, Vol. 11, No. 3, pp. 92-113, July, 1972

Economou, Steven G, Vol. 11, No. 4, pp. 151-155, Oct., 1972

Flanagan, Malachi J, Vol. 11, No. 1, pp. 3-9, Jan., 1972

Galante, Jorge O, Vol. 11, No. 4, pp. 143-150, Oct., 1972
Goodwin, Charles D, Vol. 11, No. 1, pp. 18-30, Jan., 1972

Hendrickson, Frank H, Vol. 11, No. 2, pp. 72-77, Apr., 1972
Huckman, Michael S, Vol. 11, No. 1, pp. 10-17, Jan., 1972

Johnson, Frank R, Vol. 11, No. 1, pp. 18-30, Jan., 1972

Koenig, Richard, Vol. 11, No. 1, pp. 31-34, Jan., 1972

Markey, William S, Vol. 11, No. 4, pp. 151-155, Oct., 1972
McKendall, Robert R, Vol. 11, No. 3, pp. 92-113, July, 1972

Millburn, Lowell F, Vol. 11, No. 2, pp. 72-77, Apr., 1972

Piel, Ira J, Vol. 11, No. 3, pp. 123-131, July, 1972
Perlia, Charles P, Vol. 11, No. 3, pp. iii, 131-140, July, 1972
Petasnick, Jerry P, Vol. 11, No. 1, pp. 10-17, Jan., 1972

Resnick, H.L.P, Vol. 11, No. 2, pp. 66-71, Apr., 1972
Rossof, Arthur H, Vol. 11, No. 3, pp. iii, 123-131, 131-140, July, 1972
Rostoker, William, Vol. 11, No. 4, pp. 143-150, Oct., 1972
Ryan, Will G., Vol. 11, No. 4, pp. 151-155, Oct., 1972

Schwartz, Theodore B, Vol. 11, No. 3, pp. 123-131, July, 1972
Sizemore, Glen W, Vol. 11, No. 4, pp. 151-155, Oct., 1972
Slayton, Robert E, Vol. 11, No. 2, pp. 72-77, Apr., 1972

Trobaugh, Frank E, Jr, Vol. 11, No. 3, pp. 114-122, July, 1972
Tuckfelt, Mark, Vol. 11, No. 3, pp. 114-122, July, 1972
Turner, Irene R, Vol. 11, No. 1, pp. 35-41, Jan., 1972

Valeriote, Frederick A, Vol. 11, No. 2, pp. 51-65, Apr., 1972
Vijungco, Jose, Vol. 11, No. 2, pp. 72-77, Apr., 1972

Wolter, Janet M, Vol. 11, No. 3, pp. 123-131, July, 1972

INDEX TO ARTICLES AND AUTHORS IN MEDICAL BULLETIN 1973

ARTICLES

Abstracts of publications by the staff: Vol. 12, No. 1, pp. 202-207, Jan., 1973; Vol. 12, No. 2, pp. 238-247, Apr., 1973; Vol. 12, No. 3, pp. 281-287, July, 1973; Vol. 12, No. 4, pp. 323-330, Oct., 1973

Acupuncture. See: Transcutaneous Stimulators in Pain Control

Analgesia, anesthesia. See: Transcutaneous Stimulators in Pain Control

Brainard, Dr. See: Dear Dr. Brainard—A Letter to the Founder of Rush Medical College

Commencement address. See: Rush Medical College

Comparison of Tubular Nephrosis Produced by Mercuric Chloride with Nephrosis due to N-Bromoacetyl Alpha Amino Acids. George Y. Hsu, George Kalin, G. Michael Hass, Vol. 12, No. 3, pp. 251-255, July, 1973

Coronary care. See: Immediate Prognosis in the Medical Intensive-Coronary Care Unit

Dear Dr. Brainard—A Letter to the Founder of Rush Medical College (Commencement Address). Robert J. Glaser, Vol. 12, No. 3, pp. 274-280, July, 1973

General Hospital and Nursing Home as a Focal Point for Tuberculosis Control, The. Lawerence D. Edwards and Stuart Levin, Vol. 12, No. 1, pp. 175-183, Jan., 1972

Hektoen prize. See: A Novel Bile Pigment

Hepatic porphyria. See: A Novel Bile Pigment-Porphyrin Complex

Hip: Congenital Dislocation. See: Modified Ludloff Procedure

Immediate Prognosis in the Medical Intensive-Coronary Care Unit: A Report of 607 Consecutive Patients. Philip R. Liebson, Vol. 12, No. 4, pp. 291-304, Oct., 1973

Incorporation of Amino Acids and Nucleic Acid Precursors by Cell Suspensions Isolated from Rat Liver. Patrick E. Lentz, Vol. 12, No. 2, pp. 211-221, Apr., 1973

Index to Vol. 12. Vol. 12, No. 4, pp. 331-332, Oct. 1973

Infectious disease. See: The General Hospital and Nursing Home as a Focal Point for Tuberculosis Control

Intensive care. See: Immediate Prognosis in the Medical Intensive-Coronary Care Unit

Leiomyoma: See Pedunculated Uterine Leiomyoma

Mental nerve. See: The "Numb Chin" and Neoplasia

Metastatic Carcinoma from the Cervix to the Calcaneus: A Case Report. Allan N. Levine and Mitchell B. Sheinkop. Vol. 12, No. 2, pp. 234-237, Apr., 1973

Metastatic carcinoma. See: The "Numb Chin" and Neoplasia; Metastatic Carcinoma from the Cervix to the Calcaneus

Modified Ludloff Procedure for Congenital Dislocation of the Hip. A Preliminary Report, Mitchell B. Sheinkop, Timothy Lindquist, Allan Levine. Vol. 12, No. 4; pp. 311-314, Oct. 1973

Nephrosis. See: Comparison of Tubular Nephrosis Produced by Mercuric Chloride with Nephrosis due to N-Bromoacetyl Alpha Amino Acids

Novel Bile Pigment-Porphyrin Complex Induced by Allylisopropylacetamide and Prevented by Ingestion of Lead. George Y. Hsu, Vol. 12, No. 2, pp. 222-229, Apr., 1973

"Numb Chin" and Neoplasia. Arnold D. Scheller, Jr., Floyd A. Davis, Robert E. Slayton, Vol. 12, No. 2, pp. 230-233, Apr., 1973

Nursing homes. See: The General Hospital and Nursing Home as a Focal Point for Tuberculosis Control

Pediatric Research in Russia: The Classical Period. Anatoly Bezkorovainy, Vol. 12, No. 4, pp. 315-322, Oct., 1973

Pedunculated Uterine Leiomyoma with Parasitic Blood Supply from the Superior and Inferior Mesenteric Arteries. David J. Kurti, Suresh K. Patel, Jerry P. Petasnick, Vol. 12, No. 3, pp. 269-273, July, 1973

Protein synthesis. See: Incorporation of Amino Acids and Nucleic Acid Precursors by Cell Suspensions Isolated from Rat Liver

Rush Medical College. See: Dear Dr. Brainard—

Russia. See: Pediatric Research in

Shock. See: Use of Vasoactive Drugs in

Studies on the Primary Structure of Human Serum Transferrin: A Preliminary Report. Anatoly Bezkorovainy and Dietmar Grohlich, Vol. 12, No. 1, pp. 184-187, Jan., 1973

Suggestions to Authors: Vol. **12**:208, **12**:248, **12**:288,

Sympathectomy Revisited: Retrospect and Prospect. Geza de Takats, Vol. 12, No. 1, pp. 188-201, Jan., 1973

Transferrin. See: Studies on the Primary Structure of Human Serum Transferrin

Tuberculosis control. See: The General Hospital and Nursing Home as a Focal Point

Use of Vasoactive Drugs in Shock. Richard M. Vazquez, Vol. 12, No. 3, pp. 256-268, July, 1973

Uterine leiomyoma. See: Pedunculated Uterine Leiomyoma with Parasitic Blood Supply from the Superior and Inferior Mesenteric Arteries

Vasoactive drugs. See: Use of Vasoactive Drugs in Shock

AUTHORS

Bezkorovainy, Anatoly: Vol. 12, No. 1, pp. 184-187, Jan., 1973; Vol. 12, No. 4, pp. 315-323, Oct., 1973

Davis, Floyd A: Vol. 12, No. 2, pp. 230-233, Apr., 1973
de Takats, Geza: Vol. 12, No. 1, pp. 188-201, Jan., 1973

Edwards, Lawerene D: Vol. 12, No. 1, pp. 175-183, Jan., 1973

Glaser, Robert J: Vol. 12, No. 3, pp. 274-280, July, 1973
Grohlich, Dietmar: Vol. 12, No. 1, pp. 184-187, Jan., 1973

Hass, G. Michael: Vol. 12, No. 3, pp. 251-255, July, 1973
Hsu, George Y: Vol. 12, No. 2, pp. 222-229, April, 1973; Vol. 12, No. 3, pp. 251-255, July, 1973

Kalin, George: Vol. 12, No. 3, pp. 251-255, July, 1973
Kurti, David J: Vol. 12, No. 3, pp. 269-273, July, 1973

Lentz, Patrick E: Vol. 12, No. 2, pp. 211-221, Apr., 1973
Levin, Stuart: Vol. 12, No. 1, pp. 175-183, Jan., 1973
Levine, Allan N: Vol. 12, No. 2, pp. 234-237, Apr., 1973; Vol. 12, No. 4, pp. 311-314, Oct., 1973
Liebson, Philip R; Vol. 12, No. 4 pp. 291-304, Oct., 1973
Lindquist, Timothy: Vol. 12, No. 4, pp. 311-314, Oct., 1973

Patel, Suresh K: Vol. 12, No. 3, pp. 269-273, July, 1973
Petasnick, Jerry P: Vol. 12, No. 3, 269-273, July, 1973

Sadove, Max S: Vol. 12, No. 4, pp. Oct., 1973
Scheller, Arnold D, Jr: Vol. 12, No. 2, pp. 230-233, Apr., 1973
Sheinkop, Mitchell B: Vol. 12, No. 2, pp. 234-237, Apr., 1973; Vol. 12, No. 4, pp. 291-304, Oct., 1973
Slayton, Robert E: Vol. 12, No. 2, pp. 230-233, Apr., 1973

Vazquez, Richard M: Vol. 12, No. 3, pp. 256-268, July, 1973

MFG. BY
NORDEN BINDERY
2100 W. GRAND AVE
CHICAGO, ILL. 60612